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## Original Communications

### DEVELOPMENTAL PATHOLOGY: A NEW FIELD IN MEDICINE\*†

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IN RECENT years, a new and thrilling discipline of biology and medicine has grown out of research in various fields, almost unnoticed by the medical profession: this is developmental pathology. Much fragmentary knowledge had accumulated for many years, but it has only recently been possible to integrate and understand most of it. Since the developmental processes occurring in embryonic life are more numerous and fundamental than those of later periods, developmental pathology is largely concerned with the embryo. Yet, it is obvious that some measure of development goes on and may go wrong after birth, and disturbances of postnatal life do not differ essentially from prenatal ones, as will be discussed later. Clearly separated from these abnormalities resulting in malformations are, in the minds of many pathologists, the diseases of postnatal life, as for instance those caused by infection or poisoning. However, these diseases are no more limited to postnatal life than are developmental aberrations to the embryonic period. Autopsies in still-born and newborn infants reveal an unexpectedly high incidence of necrosis, inflammation, or fibrosis in various organs, indicating the occurrence of typical disease processes in the embryo.

The relationship of malformation and disease (if such subdivision is at all permissible) is not limited to their occurrence during the same periods of life. More fundamental relations of a causal nature are known to exist in many instances. It is obvious that many malformations that are not outright lethal produce disease. As examples, the congenital interruption of bile ducts with

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consequent cirrhosis and insufficiency of the liver, or certain malformations of the heart leading to circulatory embarrassment may be mentioned. On the other hand, we have learned not so long ago that rubella during the first trimester of pregnancy causes malformations of the brain, eyes, inner ears, heart, and other organs.<sup>1</sup> A condition which cannot be definitely classified as either malformation or disease is mucoviscidosis<sup>2</sup> with its best known manifestation, cystic fibrosis of the pancreas. In this condition, the prenatal disturbances in the structure of various glands and ducts might be considered as malformations. Yet, there are indications that these changes are due to abnormal function of these glands, probably on a genetic basis,<sup>2, 3, 4</sup> or to fetal inflammation<sup>5</sup>; in other words, disease. Finally, there are genetically determined degenerative changes, the products of which are classified as malformations when they appear in early life (for instance, taillessness in mice), and as diseases when they occur late (for instance, various degenerative diseases of the nervous system). It follows from these considerations that there is no inherent difference between malformations and disease, and that all classifications, recognizing these two distinct categories, are of necessity arbitrary.

A few illustrative examples will be cited in order to demonstrate the extent of existing knowledge in developmental pathology and its usefulness to the pathologist and practicing physician. Obviously, much of the systematic and well-controlled work has been done on animals, and some of this will be mentioned because of its general significance. For more detail the reader is referred to a review which appeared elsewhere.<sup>6</sup>

Hereditary abnormalities in man are recognized in increasing numbers, and the rapidly expanding knowledge in this field<sup>7</sup> has proved useful in many cases in which eugenic advice was desired. In animals, hereditary traits afford a unique opportunity to study the biology of abnormal development in great detail because various stages of these abnormalities are readily available for description and experimentation. It should be remembered that the inheritance of abnormal traits is governed by the same laws as is the heredity of normal properties. Inherited abnormalities are reproduced just as faithfully as normal traits, and these inherited abnormalities are susceptible to modification by the influence of environment just as normal traits are. Snyder<sup>8</sup> has compiled in concise form the reasons why the expression of hereditary traits may vary among individuals who carry the genes responsible for these traits. The differences in expression are accounted for not only by the action of other genes which may increase or reduce the expression of a particular trait, but also by the action of environmental factors. These points may be illustrated by work done on some of the very well-studied hereditary abnormalities in chicks. Landauer<sup>9</sup> has bred chicks with a hereditary trait producing an abnormally short upper beak. In using those birds which showed the least effect, he was able to select his animals for the presence of modifying factors to such an extent that finally the expression of the gene for short upper beak was entirely inhibited in the great majority of birds. The following is an example of the action of environment upon the expression of hereditary malformations.

Polydactylism in the chick can be prevented in a large number of cases by reducing the incubation temperature at a certain specific time of embryonic development (Sturkie<sup>10</sup>). The embryo will then develop normal extremities.

In mammals, there are also indications of the existence of genetic and environmental modifiers. This has been demonstrated particularly in taillessness of mice<sup>11</sup> and rats.<sup>12</sup>

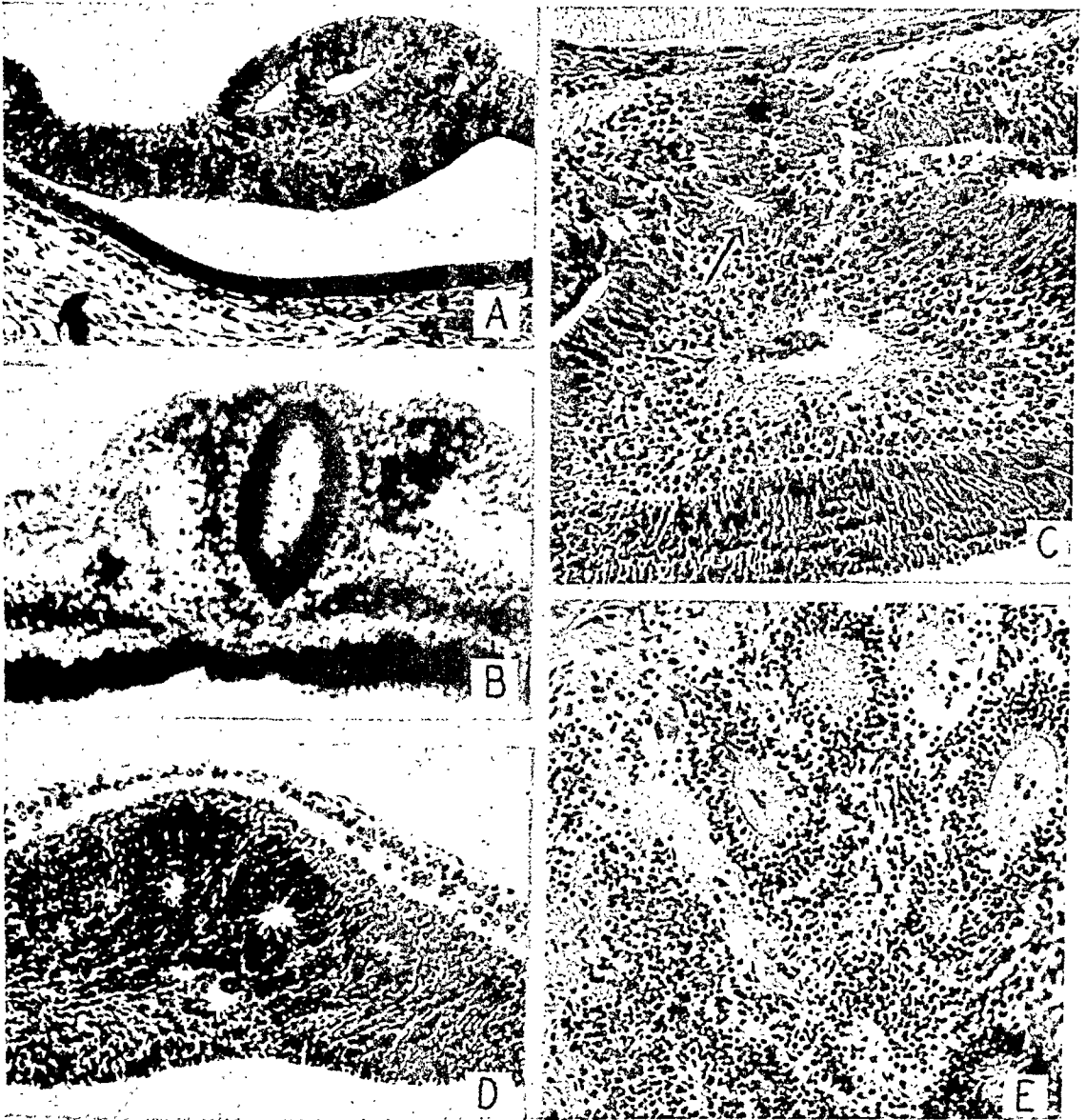


Fig. 1.—An example of similar abnormalities produced by various agents: rosettes in the retina. A, A hereditary abnormality in the chick. B, Retina of a human fetus after irradiation with x-rays (from Goldstein and Wexler,<sup>15</sup> courtesy of authors and American Medical Association). C, Rosettes in a vitamin A deficient rat embryo (specimen courtesy Dr. J. Warkany). D, Retina of a rat, one week after puncture of the eyeball at birth. E, Retina of an infant with microphthalmia.

The uterine environment of the mammalian and presumably of the human embryos is not invariably favorable. It has been shown that when embryos of mice which are homozygous for a lethal trait known as *yellow*, develop in the uterus of a normal mouse, they survive for a longer time than they would in the uterus of a *yellow* mouse.<sup>13</sup> This work was done by transplanting ovaries of *yellow* mice to others which do not carry that factor. Another investigation<sup>14</sup> in mice showed that the litter size depended on the uterine environment. In other words, the mortality among very early embryos is apparently dependent, at least in part on the uterine environment.

Just how an abnormal genetic trait produces abnormalities during development is not known. It has been suggested by many investigators that a temporary inhibition of development may cause abnormalities and that this inhibition will particularly affect certain areas which are highly susceptible at the given moment. The great susceptibility of certain parts is believed to be due to their particularly active growth and development. Similarly, environmental influences are assumed to affect most severely those portions of the embryo growing most rapidly at the moment of their action. It is only reasonable to assume that one might simulate the effect of genetic abnormalities by environmental influence, and this has actually been done, resulting in so-called phenocopies<sup>15</sup> of hereditary traits. For example, a recessive trait was found in chicks which, when present in the homozygous form, produces microphthalmia and finally leads to death of the chick about the time of hatching. In the development of the eyes, the first discernible abnormality consists of formation of so-called rosettes in the retina.<sup>16</sup> These rosettes are very small cavities in the solid tissue of the retina surrounded by a layer of cells which resembles the future layer of rods and cones (Fig. 1, *A*). It has been found that treatment of various normal embryos with x-rays<sup>17, 18</sup> results in the formation of similar rosettes (Fig. 1, *B*), and also in the development of microphthalmia. Other procedures such as avitaminosis A<sup>19</sup> (Fig. 1, *C*), or mechanical injury<sup>20</sup> (Fig. 1, *D*) which tends to reduce the size of the eyeball will also produce rosettes very much like the hereditary ones. Similar formations occur in spontaneous malformations of the eyes in man (Fig. 1, *E*).

In dealing with hereditary abnormalities, one must remember that the abnormal genotype of a given individual remains the same throughout life and that it cannot be altered at will by any experimental procedure. That explains the great tenacity with which certain abnormalities of a hereditary nature express themselves throughout life. A clinically important example is intersexuality. In some individuals, an abnormal determination of sex results in the development of various combinations of male and female structural traits in the genital organs. These combinations are so numerous and unpredictable that even the inspection of the internal genitals does not permit the physician to determine whether the individual is a male or female. The reason for this is obvious: the individual is neither male nor female. It has developed in perfect accordance with its own genotype which has determined that it will be an intersex. Since in every individual, normal or abnormal, the genetic sex has a great tenacity, it is impossible to establish in an intersex a normal male or female sex by any procedure at our command. Many individuals have been observed who showed external genitals which were more female than male in appearance. They had inguinal hernias, and when they were explored by a surgeon, testicles were found in them. It was reasoned that these testes interfered with the normal female development of the individual and the gonads were therefore removed. The effect was comparable to menopause, but none of these individuals became any more female by removal of testes than they had been before. It has therefore been suggested by biologically well-informed workers<sup>21, 22</sup> to abstain from removing the gonads of these individuals and limit oneself to such plastic and purely external interference as will make the life of the individuals more nearly normal. Another important point in this connection is that no diagnostic procedure, including biopsy of the gonad, will permit one to determine in an intersexual infant or child whether it eventually will have male or female feelings. This is another reason for interfering as little as possible with the genitals of these persons, particularly as long as their psychic sex has not adequately manifested itself.

Contrast with this the conditions in those intersexes who have a normal male or female genotype. These cases have developed abnormally because they have been subjected to hormonal influences which interfered with the normal manifestation of their genetic sex. The most common cause is a tumor of the adrenal cortex which may, at any time before or after birth, tend to reverse the sex of its bearer.<sup>23</sup> In this case, a normal genotype is present and, if one is successful in removing the cause of the disturbance, the organism will attempt by itself to revert to its normal sex.

The great permanent power of the genetic sex is also well illustrated by the following experiment in chicks. It is easy to transform male chick embryos completely into females by the injection of estrogen into the egg. If this is properly done, a male may be transformed to such an extent that morphological examination will not reveal its true genetic sex at the time of hatching. Yet, if these animals are allowed to live without any further hormonal treatment, they will eventually tend to revert to their original male sex.<sup>24, 25</sup> This happens despite the fact that at birth these chicks have ovaries which might be expected to produce sufficient female hormones to assure female development for the rest of their lives. Actually, the power of the hormones of the gonads during early periods of development has been greatly overrated. Recent investigators have concluded from many lines of evidence that male or female development of the so-called secondary sex characters in the embryo is not at all dependent on a secretion of the embryonic gonads. The gonads may be removed and the embryos will develop normal male or female traits in their absence.<sup>26</sup>

One of the most intriguing features of hereditary malformations is the appearance of complex syndromes which affect various organs or organ systems in a manner that cannot be explained by a common basis in their development. In some instances, detailed studies will reveal a common basis such as in the case of a hereditary abnormality in the rat which has been described by Grüneberg.<sup>27</sup> These rats show various skeletal abnormalities and die of pulmonary infections. A basic abnormality in the development of their cartilaginous skeleton was found, which accounts not only for the deformities of their bones but also for such changes in the ribs and in the cartilages of the respiratory passages that emphysema and pulmonary infection terminate their lives. Another instance might be mentioned in which the common basis for a great variety of abnormalities was found. A strain of mice was discovered which showed various abnormalities of the extremities, jaws, and eyes. Investigation of the embryonic development<sup>28</sup> revealed that collections of cerebrospinal fluid escape from the brain and travel as blebs under the epidermis of the embryo. The blebs keep moving until they are trapped at some point. They do permanent damage only at those points from which they can no longer escape, such as the feet and jaws as well as the region of the eyes. When the fully developed malformations are seen, the blebs have long disappeared and no one could determine the mechanism of origin from the study of the fully developed condition alone.

In other instances, various manifestations of an abnormal genetic trait appear at a stage which we cannot apprehend with our morphological methods. As a result, a variety of seemingly unrelated changes are present at the earliest stages at which we can determine abnormalities in the development of these individuals; this is the case in the *Creeper* chick. Hamburger<sup>29</sup> has compiled our present knowledge of this abnormal trait and has shown that four different abnormalities appear in the homozygous *Creeper* embryo and cause the defects of blood vessels, skeleton, and eyes.

One mechanism of the development of hereditary abnormalities must be mentioned in more detail because it also occurs in postnatal periods. This is the degeneration of previously normal-appearing parts. We know that during postnatal life a great variety of degenerative hereditary diseases of the nervous system, the muscles, and other parts of the body appear and the morphological sequence of stages has been studied in considerable detail in several instances. Retinitis pigmentosa is a well-known example, thoroughly investigated from the genetic and morphologic points of view.<sup>30</sup> Old-age changes may have a similar genetic background. Gorer<sup>31</sup> found that three inbred strains of mice develop distinctly different changes in the kidneys, in a high proportion of cases, as they grow old. One shows hyperplasia of Bowman's capsules; the second strain develops necrotic lesions in the papillae, and cysts in the cortex; and in the third one there is hyaline degeneration of the connective tissue stroma.

During the past few years it has been found that processes similar to these heredodegenerative changes may occur in the early embryo and account for conditions which anyone would consider as malformations. There are several hereditary traits which determine the absence or reduction of the tail in mice<sup>32</sup> as well as in chicks.<sup>33, 34</sup> Some of these have been studied embryologically and it was found in every case that the primordium of the tail is at first present as in any normal embryo and then, at a given stage which is strictly characteristic for each of these hereditary traits, degeneration sets in, the tissue becomes necrotic, and finally sloughs off. In another instance involving defects of the feet and ears in rabbits, hemorrhage and necrosis occur, beginning on the sixteenth day of gestation, and result in the loss of previously well-developed parts of the body.<sup>35</sup> These examples illustrate best the fallacy of the method of the old teratologists who sought to establish the manner of development of a malformation by studying only the fully developed abnormality and determining the presumptive stages in embryonic life in which the particular organ failed to undergo its normal development. None of these speculations took into account the possibility of secondary degeneration of a previously normal primordium. In this connection, it is interesting to note that, in mice as well as in rats, there is a hereditary condition of rodless retina. In mice, the rodless retina is due to a failure of differentiation.<sup>36</sup> In rats, however, the retina is at first normally developed and then undergoes secondary degeneration after birth.<sup>37</sup>

Most of the mutations which produce hereditary abnormalities arise spontaneously. There are but a few examples in which mutations have been produced in higher animals, e.g., by treatment with x-rays. It is generally acknowledged that the chances of producing such mutations in man are very low;<sup>38, 39</sup> yet, with the increased use of biologically highly active methods in medicine it becomes important that we realize the possibility of danger to the genetic mechanism which may manifest itself in the progeny of the treated person. This should be remembered particularly when x-rays, or such substances as nitrogen mustard, are used in a manner in which they may affect the germ cells in the gonads without completely destroying their activity. It is also important to distinguish these effects on germ cells from those upon the developing embryo which do not affect the genotype; the latter will be briefly mentioned below.

Developmental abnormalities caused by influences of the environment are of relatively little importance in the mammalian embryo. The uterine environment protects the embryo very well although this protection is not as complete as one might believe at first glance. We have already mentioned that the uterine environment in itself is not uniformly favorable and may have an effect upon the development of the embryo.

Most of the physical and chemical agents which may influence development have been studied in animals other than mammals. Some of this work should be briefly mentioned in view of its significance for the understanding of the mechanisms of abnormal development in general. It is obvious that mechanical influence destroying or removing parts of the embryo may result in deformity. There is no need for elaborating on this subject. Work with chemicals, however, is of great interest. Long ago, Werber<sup>40</sup> produced very severe malformations in fish embryos by organic substances, for instance, acetone, which may also occur in the human organism. These malformations may assume bizarre forms and in some cases isolated eyes have been found growing on the surface of the yolk. Werber's<sup>41</sup> suggestion, that in man malformations may be due to the same cause, is very improbable because sufficient concentrations of acetone can hardly be assumed to be compatible with pregnancy in the human species. Much work of general interest has been done in amphibians with lithium salts and in chicks with selenium compounds. A recent investigation of Gillette and Bodenstein<sup>42</sup> in newts has served to confirm the above-mentioned hypothesis that rapidly growing tissues are particularly sensitive to damaging agents. These authors treated newt embryos with one of the nitrogen mustards and found that rapidly dividing cells are selectively affected. It could even be shown that among tissues of the same histologic type those portions which grow rapidly are severely damaged, whereas others, which are quiescent, escape injury.

The effect of various deficiencies has been studied in the embryos of mammals. Warkany and his co-workers<sup>43</sup> studied the effect of riboflavin deficiency upon rat embryos and found that various skeletal abnormalities as well as cleft palate may result. The production of eye malformations in rats by maternal vitamin A deficiency has also been investigated.<sup>43</sup> Reports of human cases of fetal rickets and scurvy are inconclusive, but there can be no doubt that vitamin deficiencies may have an effect upon the human fetus.

Oxygen deficiency may affect the older embryo whenever oxygenation of the mother's blood or circulation of the embryo's own blood is impeded. It occurs most frequently during labor, and at that time some degree of it is normal and well tolerated. However, excessive anoxia may result in damage to the brain, lungs, and possibly other organs. Brain damage and its pathological and functional manifestations have been described in human newborns by Schreiber<sup>44</sup> and others, and in experiments with newborn guinea pigs by Windle and co-workers.<sup>45</sup> Histologically, necrosis and hemorrhage are found. The lungs may suffer by the aspiration of vernix and meconium when anoxia stimulates strong respiratory efforts in utero. While some lungs appear to tolerate moderate amounts of these materials fairly well, others will be unable to expand when the bronchioles are lined with thick, fatty vernix,<sup>46</sup> and still others will become the seat of pneumonia shortly after birth.<sup>47</sup> In young embryos of lower animals, severe malformations can be produced by anoxia; this is not known to occur in man.

It is common knowledge that irradiation with x-rays may severely damage the fetus, and result in malformations of various organs.<sup>48</sup> Similar results have been obtained experimentally in mammals.<sup>49</sup> It has been established that irradiation at different periods of embryonic development results in different and fairly well-defined types of malformations.

In malformations, just as in normally developing organs, the development of one part often depends on that of an adjacent part. On the one hand, this insures proper relations of the parts concerned; on the other hand, abnormalities in development may extend far beyond the original limits of the



damage by similar mechanisms of dependent development. The following example concerning the urogenital tract will serve to illustrate this point. In the normal embryo, the mesonephros as well as the permanent kidney and the uterus depend for their normal development on a normal Wolffian duct. If during development the growing end of the Wolffian duct is damaged in a minute area, not only the entire duct fails to develop from that point on, but the other organs which depend on it for their development will also be absent (Fig. 2, A). The result is a complex of abnormalities which can be produced in chick embryos by destroying the growing end of the Wolffian duct (Fig. 2, B) and which also occurs relatively commonly in man and mammals as a spontaneous malformation.<sup>50</sup> This syndrome comprises after completed development, in the male, the absence of all or part of the epididymis, the ductus deferens, the kidney and ureter; and, in the female, all or part of the epoophoron, the tube, one-half of the uterus, and again the kidney and ureter (Fig. 2, C). All these organs can thus be damaged indirectly by destroying a minute group of cells at the growing end of the Wolffian duct in the early embryo.

Other correlations between developing organs are mediated by hormones. These substances play an important role in directing the development of various parts of the body before and after birth. Examples of endocrine disturbances are so well known that they need not be quoted here.

There are correlations between the nervous system and the organs supplied by it. These are of much greater importance after birth than they are in the embryo. Yet, even during prenatal development such influences are known to exist. Development of extremities will be inhibited to some degree when they are not properly innervated<sup>51</sup> and, in turn, development of certain portions of the spinal cord will be altered if the organs normally supplied by that portion develop abnormally.<sup>52, 53</sup>

Finally, we come to so-called diseases of the fetus, that is, conditions which are comparable to diseases of postnatal life. The mere existence of these conditions shows that the protection of the human embryo is not fully dependable and that it is worth while to direct one's attention toward supervising the environment of the developing fetus in utero. One group, namely, vitamin deficiencies, has been briefly mentioned above. Another one concerns inflammatory processes. The problem of fetal inflammation and its relation to malformations has received extensive consideration in the field of pathology of the heart. We know that in certain congenital abnormalities of the heart conditions prevail which closely resemble the scarring after postnatal inflammation, for instance, rheumatic heart disease. There has been much argument as to whether those fetal conditions are, or are not, the outcome of fetal inflammation. It is quite possible that, as some authors assume, the existence of a thick layer of fibrous tissue under the endocardium (Fig. 3, A, B) is a developmental aberration rather than the result of inflammation.<sup>54, 55</sup> On the other hand, many observers have studied cases in which there was a diffuse scarring that involved all layers of the wall of the heart combined with areas of calcification and of inflammatory cellular infiltration. It is difficult to escape the conclusion that in these cases the findings are the result of a fetal inflammation.<sup>56</sup>

Much publicity has been given to the observation that a disease which was generally believed to be harmless can produce severe malformations of the fetus when it occurs during the first trimester of pregnancy. This is the case in rubella and occasionally in other virus diseases.<sup>1</sup> There is no agreement as to the percentage of cases in which malformations result, but the number of cases is certainly sufficiently large to warrant careful consideration and, if possible, prevention. The organs most prominently affected by ab-

normalities are the brain, eyes, and heart. Other organs, such as the inner ear and the teeth have also been found to be defective. Only a very small number of these cases have been examined at autopsy. The changes are not very conspicuous. In the eyes, a characteristic form of cataract which is believed not to occur in any other condition has been described by Swan.<sup>57</sup> The changes in the brain have, to the best of my knowledge, not been thoroughly investigated.

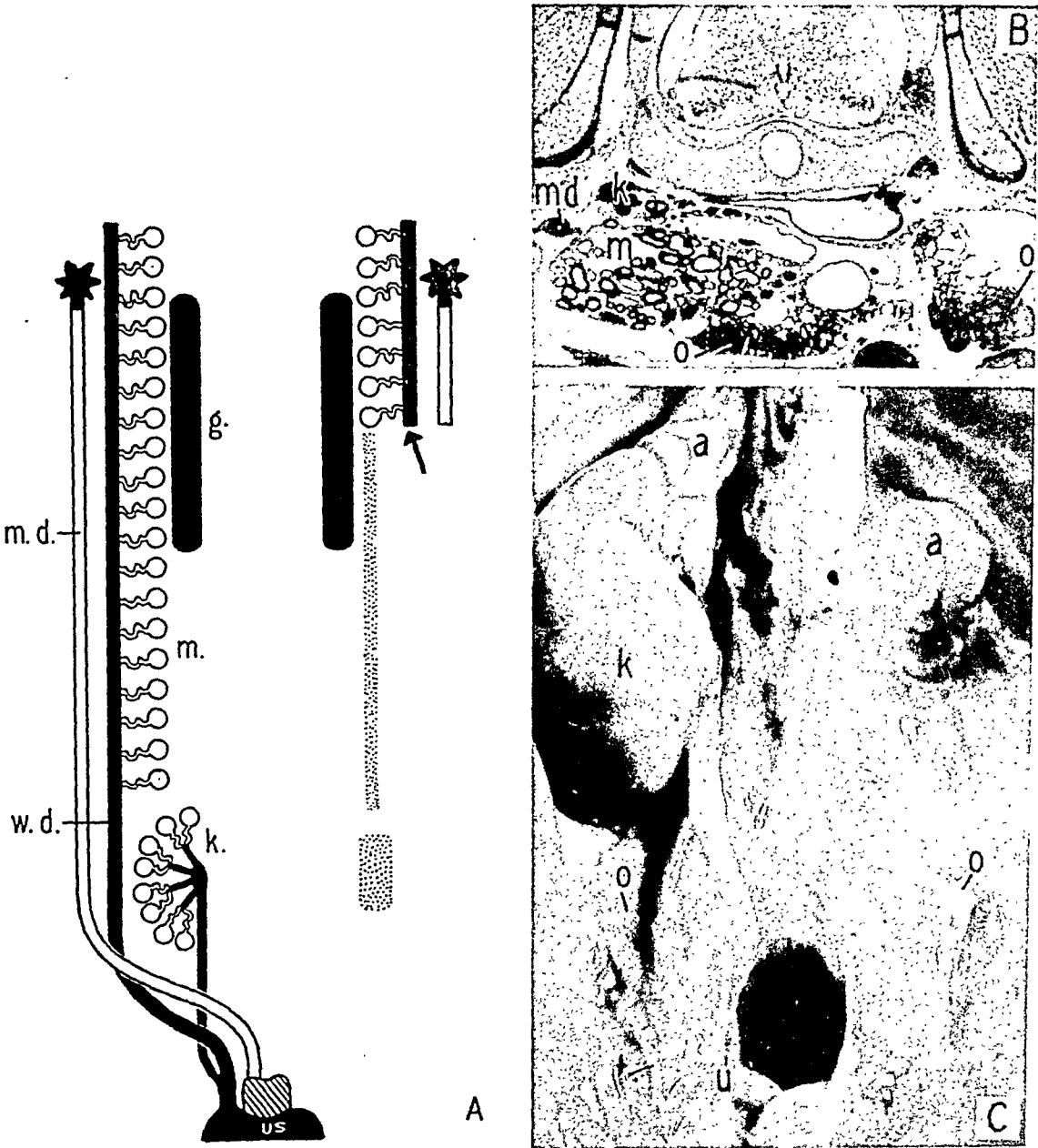


Fig. 2.—One primary abnormality causing a syndrome of malformations by dependent development. The diagram (A) shows on the left side the urogenital organs of the embryo developing normally. The parts which develop independent of others are shown solid black; those which depend on these parts are outlined. The right side of the diagram shows the multiple effects of termination of growth of the Wolffian duct at the arrow. All other defects are sequelae of this event. This can be done experimentally in chick embryos by destruction of the growing end of the duct. The result is shown in Fig. 2, B. The corresponding human malformation in a female infant is shown in Fig. 2, C. *a*, adrenal; *g*, gonad (ovary or testis); *k*, kidney; *m*, mesonephros; *m d*, Müllerian duct; *o*, ovary; *t*, tube; *u*, uterus; *u s*, urogenital sinus; *w d*, Wolffian duct.

In the heart, patent ductus arteriosus is the most common finding. The so-called fetal endocarditis or myocarditis which was mentioned above, is not found in this condition. We have no knowledge whatever of the mechanism by which the embryo is damaged if the mother acquires rubella during the first trimester of pregnancy. We do not know whether the disease affects the embryo directly, or just its environment, which may secondarily have its effect upon the developing organs of the embryo.

Another infection which appears to be entirely asymptomatic in most adults but causes severe disease in the fetus is toxoplasmosis. In contrast to rubella, toxoplasmosis is known to affect the fetus directly and the organism, a protozoan, has repeatedly been found in fetal tissues, surrounded by areas of tissue destruction and inflammation. Many organs may be affected, among them the brain, eyes, and heart.<sup>58, 59</sup>

Other instances of fetal diseases manifesting inflammation, necrosis, and fibrosis may be found in surprisingly many cases if one studies stillborn and newborn infants carefully at autopsy. In more than 10 per cent of all stillborn infants and newborn infants less than three days of age, one finds indications of a disease which must have occurred before birth.

The following is a selection of examples from the material gathered during two years at Kings County Hospital, and more recently in a survey of neonatal pathology to which many hospitals in Brooklyn have been contributing their material. Cases of fetal syphilis were not common and some of the manifestations described in all textbooks were not seen. However, two unusual cases were examined, which showed severe changes in the heart and intestine.

Several examples of the so-called fetal endocarditis were found (Fig. 3, *A, B*), and in some of them the microscopic findings strongly suggested that disease processes rather than primary developmental abnormalities had caused the changes.

In a two-month-old infant there were severe calcification and proliferation in the wall of the coronary arteries and almost all other arteries of large and medium size which could be examined (Fig. 3, *C*). The findings closely resemble those in other cases reported in the literature, and in addition very early stages of the abnormality were seen in the media of the aorta.

Focal necrosis in the media and adventitia of coronary arteries (Fig. 3, *D*) was found at first in two newborns, and when sections from other infants were re-examined, the number of cases rose to eighteen. The cause and the significance of these lesions are unknown.

The liver appears to be the seat of pathologic changes in many instances. Extensive necrosis of liver tissue (Fig. 4, *A*) was found in several stillborn and newborn infants. Two infants aged two and three days, respectively, died with cirrhosis of the liver, without evidence of obstruction of bile ducts (Fig. 4, *B*). An infarct-like area of necrosis with proliferation of granulation tissue at its borders (Fig. 4, *C*) was present in the liver of a 10-day-old infant and in several instances there were foci of replacement of liver tissue by connective tissue.

The pancreas of two stillborn infants showed acute inflammation with extensive infiltration by polymorphonuclear leucocytes (Fig. 4, *D*). In a number of other cases a large area of the pancreas was infiltrated, and the glandular tissue largely replaced by lymphoid tissue.

In one very premature infant measuring 28 cm. the peritoneal cavity was completely obliterated by fibrous adhesions. A small umbilical hernia was present. Indications of acute and chronic inflammation were seen in many

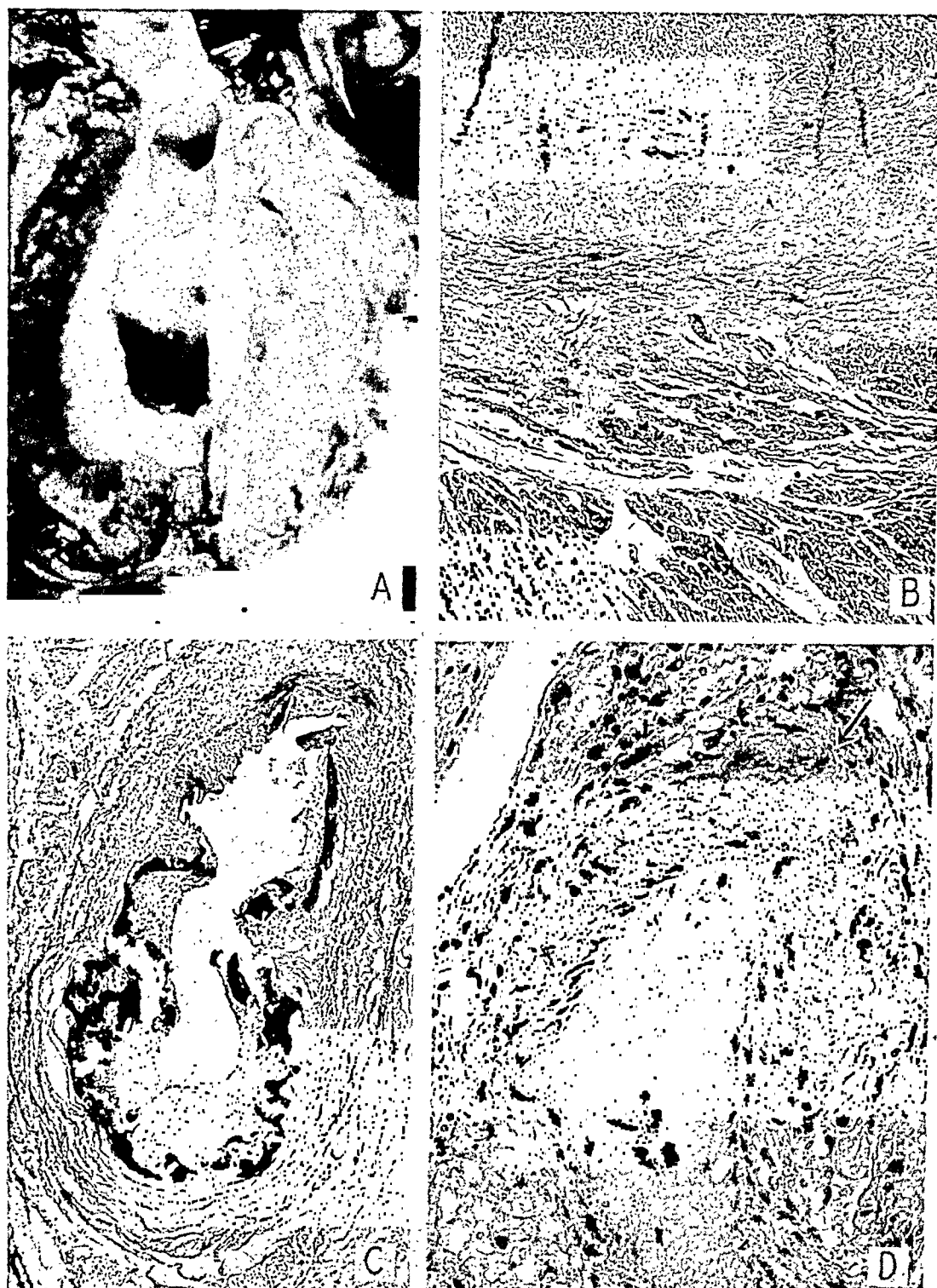


Fig. 3.—Fetal pathology of the heart. *A*, So-called fetal endomyocarditis, showing fibrous thickening of the endocardium of the left ventricle, and of the valves: *B*, A section of the same heart, with the thickened endocardium in the upper portion of the field, and part of the myocardium below. *C*, Calcification and intima proliferation in a coronary artery of a 2-month-old infant. *D*, necrosis in the media of a coronary artery in a stillborn infant.

parts of the body. They included, among others, the presence of numerous lymph follicles in abnormal locations.

It is extremely difficult to interpret most of these conditions because intra-uterine life protects the embryo not only to some extent from damage, but also from examination by the physician. Information about the previous history

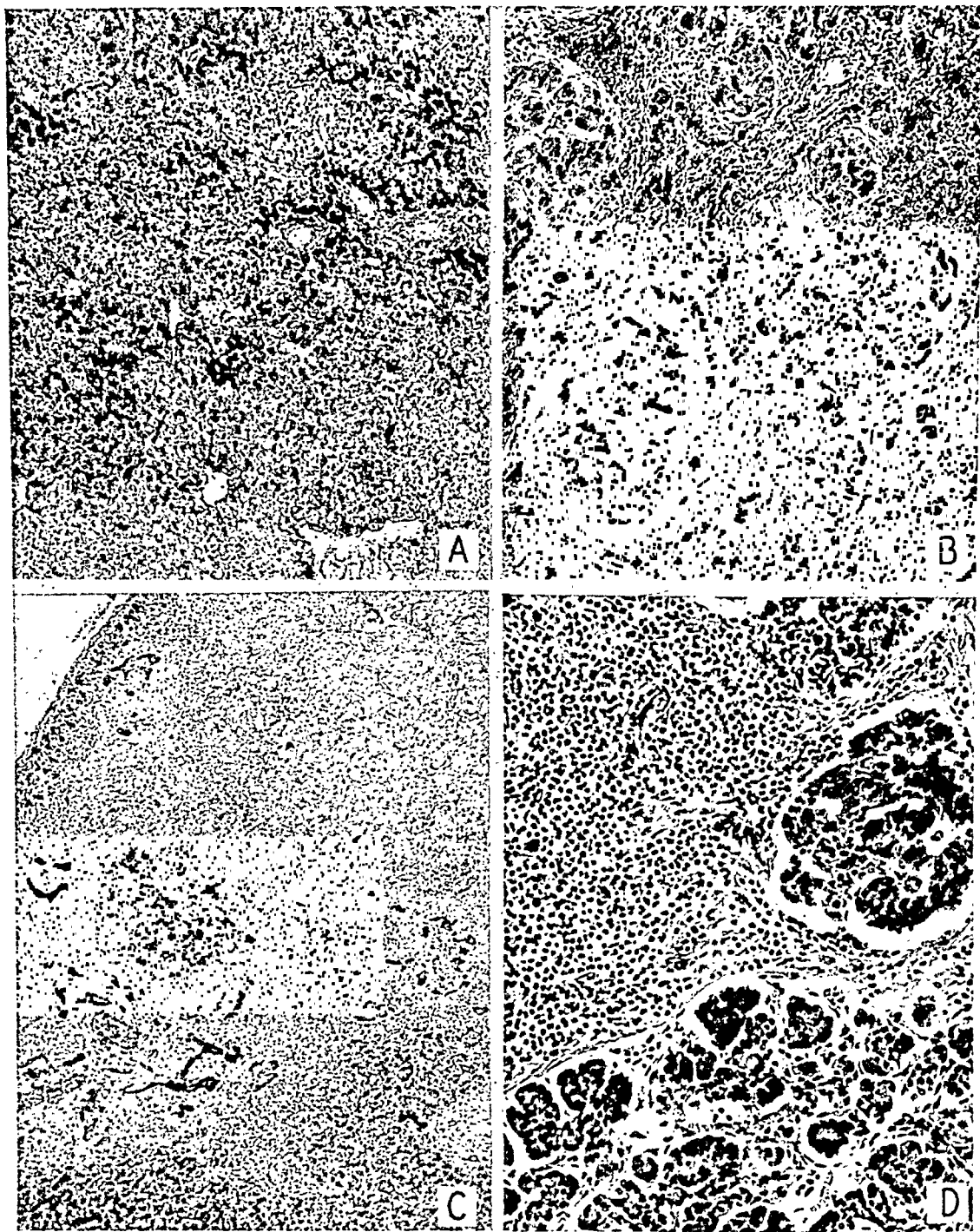


Fig. 4.—Fetal pathology of the liver and pancreas. *A*, One of many areas of necrosis in the liver of a 1-day-old infant. *B*, Advanced cirrhosis of the liver in a 3-day-old infant. *C*, Healing stage of an area of necrosis in the liver of an 8-day-old infant. *D*, Acute pancreatitis in a stillborn infant.

of these cases is, therefore, usually inadequate. In spite of this handicap, considerable advances have recently been made. This is true particularly with regard to the causes of several types of abnormalities which arise before or at birth, and affect the brain and the sense organs. A summary of recent and older information,<sup>60</sup> which also contains references to the pertinent literature, includes the following causes of mental deficiency, blindness, and deaf-mutism:

CAUSE	MENTAL DEFICIENCY	BLINDNESS	DEAF- MUTISM
<i>Genetic.—</i>			
Mutations	+	+	+
Heterospecific pregnancy	+	-	-
<i>Environmental, Prenatal.—</i>			
Infection: Syphilis	+	+	+
Toxoplasmosis	+	+	-
Rubella	+	+	+
Deficiency: Cretinism	+	(+)	+
Mongolism	+	(+)	-
Anoxia	+	-	-
Vitamin A	-	+	-
<i>Paranatal.—</i>			
Mechanical birth injury	+	-	-
Anoxia at birth	+	-	-

\*Only in animal experiments.

The fact that we have learned so much during recent years about the mechanisms underlying abnormal development and that we have discovered the causes of several common developmental abnormalities in man shows that developmental pathology is now a field of practical significance to the physician. Not many years ago prenatal abnormalities were only the subject of doctors' theses and insignificant case reports. Today, our knowledge of these conditions has helped save many lives, and basic information now at our command should assure us of great advances in prevention and therapy in the near future.

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# X-RAY VISUALIZATION OF THE PLACENTA: EXPERIENCES WITH SOFT-TISSUE AND CYSTOGRAPHIC TECHNIQUES IN THE DIAGNOSIS OF PLACENTA PREVIA

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IT IS an established fact that the placenta can be visualized in soft-tissue x-ray films in over 90 per cent of all women who are in the third trimester of pregnancy. This was forecast by Speidel and Turner<sup>1</sup> in 1924. In a paper dealing chiefly with x-ray visualization of the uterus and adnexa with the aid of artificial pneumoperitoneum, they stated: "It should be possible, by means of the roentgenogram, by the relation that the head of the fetus bears to the lower segment of the uterus, to determine the degree of encroachment of the placenta upon the internal os, and whether we have a central, lateral, or marginal placenta previa."

During the past several years at the Boston Lying-in Hospital we have made x-ray studies of all cases of uterine bleeding and of transverse or oblique position of the fetus occurring during the third trimester of pregnancy. The purpose of this paper is to report our experience regarding the x-ray diagnosis of placenta previa through the use of the soft-tissue technique introduced by Snow and Powell<sup>2</sup> and the cystographic method first described by Ude, Weum, and Urner.<sup>3</sup>

## Historical

There has long been interest in the determination of the position of the placenta in the uterus. In 1898, Holzapfel,<sup>4</sup> working at the Frauenklinik at Erlangen, studied 107 placentas with their attached membranes, using a flotation and sac distention method in a tank of water. He found that 39.2 per cent of the placentas had been located chiefly on the anterior wall of the uterine cavity, 42 per cent had been on the posterior wall, 13 per cent had been implanted principally in the region of one or the other Fallopian tube openings, 4.7 per cent had been on one of the lateral walls, and in one case, or 0.93 per cent, the placenta had chiefly occupied the lower uterine segment. Torpin,<sup>5</sup> using the same technique, more or less duplicated these findings in 1938.

The first presented case we could find in the world literature in which the human placenta, in situ in its natural state, was visualized in an x-ray film without the use of radiopaque media is that reported by Baumann<sup>6</sup> in 1930. In a general paper on roentgenologic diagnosis during pregnancy and labor, he included a reproduction of an x-ray which showed the fetus to lie in transverse position with no fetal parts in the lower uterine segment. He stated that the placenta was visible on the film itself, but the reproduction is poor and does not actually appear to show it. He made no reference to this case in the paper itself, merely referring to it in the caption under the picture as follows: "Transverse presentation as a consequence of placenta previa centralis. Placenta visible on the film. Cesarean section done."

Great stimulus was given to the study of x-ray visualization of the placenta later in 1930, however, by the appearance of a paper by Menees, Miller and Holly.<sup>7</sup> They introduced a technique which they termed "amniography." This consisted of the addition of a denser contrast medium to the amniotic fluid in order to increase the x-ray density of this liquid so as to make it stand out in sharp contrast to the fetus and placenta. They injected about 10



c.c. of a 1:1 solution of strontium iodide through the anterior abdominal wall, uterine wall, and fetal membranes into the amniotic sac. After waiting for thirty to sixty minutes, in order to permit even diffusion of the radiopaque medium, they took anteroposterior and lateral films with the patient recumbent. These films, as reproduced in their article, demonstrated clearly the position of the placenta. The fetus was so well outlined that the scrotum in several males was plainly visualized. Proof of the fact that the fetus actively swallows amniotic fluid was demonstrated by a well-outlined radiopaque fetal stomach in every case. Certain films even showed cross sections of loops of umbilical cord encircling the neck and buttocks of the fetus. In their series of twenty-one cases there were no injurious or toxic effects to the mother, but in one case the placenta was perforated and a 6-month fetus was expelled thirty hours later. They made no mention of how many mothers went into labor following the injection.

Kerr and Mackays<sup>8</sup> utilized this method in studying twenty cases of severe bleeding in women whose pregnancy was of twenty-four or more weeks' duration. In the first ten cases they, too, injected strontium iodide, but in three of them, who were in the twenty-fourth week, the fetal movements and heart sounds ceased, and the patients shortly delivered dead fetuses. They injected each of the next ten cases with 20 c.c. of Uroselectan-B, and stated that they were unable to demonstrate that the use of this drug caused any ill effects in the mother or fetus in this short series. They took lateral and anteroposterior views of the uterus thirty minutes after the injection and were able to detect the position of the placenta in eighteen of the twenty cases. Likewise they could demonstrate loops of cord and the fetal scrotum in some films. A subsequent check of the position of the placenta at the time of delivery revealed them to have been correct in each instance as to its localization by x-ray. In ten cases, labor began in from a few hours to five days following the injection. Four of the infants in their series were born during the twenty-fourth week of pregnancy and succumbed. The remaining sixteen survived even though many were premature. This technique was repeated by Burke,<sup>9</sup> whose best results were obtained with the use of Uroselectan-B. In one case the films were used in deciding in favor of cesarean section as a method of delivery, since the lower placental border was seen to encroach upon the general region of the internal cervical os. Since he found that labor was induced by the injection of Uroselectan-B, he used it as a method of induction in twenty-seven additional cases, obtaining successful results in twenty-six of them. The case that failed to go into labor was a patient with hydramnios. The onset of labor followed in from two to seventy-two hours, the average time of elapse being twenty-three and one-half hours.

The chief objections to uterine puncture for amniography are the possible danger of injury to the intestines, and of trauma to the fetus, placenta, or umbilical cord. The taking of such risks is certainly not justified in view of the efficiency of the safer methods of x-ray placentography now in use.

The important milestone in the development of techniques for x-ray visualization of the placenta came with the publication, in January, 1934, of a paper by Snow and Powell.<sup>2</sup> They described the simple procedure of taking anteroposterior and lateral films of the uterus with the patient recumbent. Without any special preparation of the patient, they employed a technique of relatively high voltage and short exposure time, and achieved a sufficient soft-tissue effect to allow ready visualization of the placenta. In the sixty routine cases upon which this method was employed, the position of the placenta was generally demonstrable as a long, elliptical thickening of the uterine wall, not occupied by fetal parts, and lying wholly within the ovoid shadow of the uterus. Snow claimed that the placenta could usually be differentiated from the liquor amnii because, "consisting of tissues and blood, [it] causes greater obstruction to the roentgen rays than the amniotic fluid, which is of low specific gravity." The experience of other workers,<sup>10, 11</sup> including ourselves, has not borne out the possibility of making this fine distinction, but such is seldom necessary except in cases of hydramnios.

One month following the paper by Snow and Powell another major contribution was made by Ude, Weum, and Urner.<sup>3</sup> They reported a case in which an anteroposterior film of the uterus of a woman in the third trimester of pregnancy showed the head displaced upward

from the pelvis and to the right. They also noted that a mass was lying on the left side of the lower uterine segment, and that it extended down beneath the head, coming between it and the bladder. The bladder had only a small amount of urine in it, but was visualized nevertheless. They made the diagnosis of placenta previa, and it was substantiated at cesarean section. This is the first x-ray diagnosis of this condition that we can find in the American literature. In subsequent cases, Ude and his co-workers injected the bladder with sodium iodide solution, thus introducing x-ray cystography as an adjunct aid in the localization of the placenta and the diagnosis of placenta previa.

In the years since the pioneering cited in the foregoing, many other workers have utilized and developed the original methods of Snow and of Ude, but in this country in recent years there have been no published papers reporting the use of the amniography technique of Menees, et al., Kerr and Mackay, and Burke.

In subsequent papers, Snow<sup>12</sup> and Snow and Rosensohn<sup>13</sup> reported the demonstration by x-ray of premature separation of the placenta, late extrauterine pregnancy (in one instance he demonstrated a thickened amniotic sac), some tumors complicating pregnancy, and, when the bladder had been injected with from 150 to 200 c.c. of air, placenta previa. In a further paper on cystography, Ude, Urner, and Robbins<sup>14</sup> reported forty-four new cases in which they injected 40 c.c. of sodium iodide solution into the bladder, and further prepared the patient by low colonic flushes in order to empty the lower bowel of feces and gas. They took 14 by 17 inch anteroposterior films, from which they made the diagnosis of central placenta previa in four cases and partial previa in one, the other thirty-nine being negative for placenta previa. The clinical findings from this group showed that forty cases were negative for placenta previa, while three had central previa and one had partial previa. Their one error was on the positive side and thus was not dangerous. The clinical result of this low incidence of error, state Ude and his co-workers, is that their obstetricians have never been misled into cesarean section, but have often been strongly fortified to proceed with surgery when the suspected clinical findings of placenta previa were confirmed. Surgical procedures should not be carried out solely on the basis of placentography, they warn, and the roentgenologic opinion should be used by the clinician purely as corroborative evidence.

### Recent Studies

The literature contains the reports of many other subsequent workers (McIver,<sup>15</sup> McDowell,<sup>16</sup> Hall, Currin and Lynch,<sup>17</sup> Prentiss and Tucker,<sup>18</sup> Beck and Light,<sup>19</sup> Dippel and Brown,<sup>20, 21, 22</sup> Lloyd and Samuel,<sup>23</sup> Buxton, Hunt and Potter,<sup>24</sup> Manges-Smith,<sup>25</sup> McCort, Davidson and Walton,<sup>26</sup> Scheetz, Good and Hunt,<sup>27</sup> and Bishop<sup>10</sup>) who have used either the soft-tissue or cystographic technique, or both. The chief clinical importance of the methods, naturally, is the making of a positive or negative diagnosis of placenta previa. Some have found, in making cystographic studies, that the use of air in the bladder, instead of a radio-paque liquid, is of great advantage in that no part of the fetal head is obscured and a more exact picture of the thickness of the soft tissues between the head and the "black" bladder shadow is obtained on the film. Others advise the use of varying amounts of 12.5 per cent sodium iodide solution, and take anteroposterior, lateral and, sometimes, oblique views. Three writers<sup>19, 24, 10</sup> have reported good results from taking anteroposterior precision stereoscopic films of the bladder, which they found to be of particular advantage in diagnosing placenta previa in cases with breech presentation. On anteroposterior cystographic films, in cephalic presentation without placenta previa, the usual distance of the head from the bladder shadow has been determined<sup>18</sup> to range between 1.1 and 1.3 cm. This space contains the fetal membranes, the wall of the lower uterine segment, the 2 vesical peritoneal layers, and the thickness of the bladder wall itself. When some additional soft-tissue mass is seen to be interposed between the head and the bladder shadow, increasing the distance between them or displacing the head appreciably upward or aside from its usual roughly central position in the pelvis, one must immediately be suspicious of the presence of placenta previa.

The reported success in accurate localization of the placenta in some fairly large series of cases varies roughly between 85 and 97 per cent. In a series of 92 women with third

trimester bleeding, Dippel and Brown,<sup>22</sup> using only the soft-tissue technique, found no errors in their roentgenologic localization of the placenta in the 53 instances in which its position was checked by reliable clinical methods. There were eleven cases of placenta previa in their series, all of which were correctly diagnosed by x-ray. The soft-tissue technique alone, report Buxton, Hunt and Potter,<sup>24</sup> gave accurate visualization of the placenta in 86.1 per cent of a series of 108 cases of painless bleeding in the third trimester. By using the soft-tissue method and cystographic studies where indicated, they were able to locate the placenta accurately in 97.6 per cent of all cases so studied. In this series they had seventeen cases of placenta previa, sixteen of which were correctly diagnosed by x-ray. Bishop<sup>10</sup> states that in properly taken films the diagnosis, "negative for placenta previa," should achieve an accuracy of 97 per cent or better, if care and judgment are exercised in their reading.

Successful results in x-ray placentography can be obtained only when the obstetrician and roentgenologist work together in a harmonious team. As Matthews<sup>28</sup> stated: "The obstetrician must take the lead and exhibit the proper amount of enthusiasm, for certainly the roentgenologist cannot be expected to know when roentgenography is indicated in a given obstetric case. It would seem, therefore, that the future of this very important help in better diagnosis is entirely in the hands of the obstetrician." "The method requires some study and observation and special interest on the part of the roentgenologist as well as cooperation of the obstetrician to show results," writes Manges-Smith.<sup>25</sup>

### Technique

At the Boston Lying-in Hospital we have used an x-ray technique essentially similar to that reported by Dippel and Brown.<sup>20</sup> When compared with the regular technique for taking roentgenograms of the abdomen, it differs chiefly in that a slightly higher voltage and lower exposure time are employed. In taking films of the pregnant uterus with the patient lying flat on the table, we use a regular intensifying screen and a 14 by 17 inch film. We vary our KVP between 75 and 82, depending on the degree, if any, of obesity. With our machine we use 100 Ma. and an exposure time of 1 to 2 seconds, whereas Dippel and Brown used 50 Ma. for 4 seconds. This factor can be varied according to the range of the equipment, but we prefer to use the higher Ma. and the shorter time exposure as it decreases the chance of fetal movement showing on the film. Dippel and Brown used a tube-film distance of 42 inches, whereas we have always taken our films at 40 inches. We employ our regular Potter-Bucky grid, but no filters nor special roentgen-tube equipment are necessary. In developing our films we rely chiefly on time, varying it slightly, if necessary, according to the usual indications. We have not found it necessary to develop the films by sight, as recommended by Carty.<sup>29</sup> Along with other workers in this field, we believe that almost any average x-ray equipment, if properly used, will give adequate soft-tissue films.

We have gradually evolved our technique, and now recommend taking the first film with the patient lying on her side (See Fig. 1, Film A). We try to get her to keep her legs unflexed at the hips as much as possible so that the upper thighs will not overlie the lower uterine segment (See Fig. 2, Film B). If the first lateral film does not show the placenta, or appears to show only an edge of it, we place the patient on the other side, either with the transverse axis of the pelvis perpendicular to the table top or at some degree of obliquity to it, according to the suggestive findings of the first film. Since about 85 to 90 per cent of placentas lie either on the anterior or posterior wall of the uterus<sup>4, 5, 22</sup> the lateral film is usually sufficient. In some cases, again follow the suggestion of the first film, we take the second plate with the patient lying flat on her back, as this will allow visualization of placentas which lie in part or in whole on a lateral wall of the uterus (See Fig. 3, Film B). The whole point is that, in order to have the placenta show on the film, we must endeavor to secure, as nearly as possible,

*an edgewise view of its central vertical axis.* In some cases, where the presenting part appears to be riding above or to one side of the inlet of the true pelvis, we will take lateral and/or anteroposterior films of the patient in the standing position, and, in most of these cases, providing the patient's bladder is empty, gravity alone will bring the presenting part downward to a closer approximation with the pelvic inlet (See Fig. 1, Film B), or may even bring about some engagement of the part. Anterior over-riding of the symphysis pubis by the head has been noted in patients who have relaxed anterior abdominal walls and postural



A.

B.

1. In the two above films the placenta lies low on the posterior uterine wall; they offer a comparison between partial and marginal placenta previa.

Film A: C. D., Unit No. 39282, X-ray No. 22981, a 32-year-old gravida ii, para i, had a small amount of painless bright vaginal bleeding in her 25th week, and again in her 31st week, at which time the above x-ray was taken. The roentgenologic diagnosis of "posterior wall placenta, with partial placenta previa" was made. She bled again, in greater amount, in her 33rd week, and vaginal examination revealed her to have a partial previa. Immediate classical section was done, and the placenta was found to lie low on the posterior uterine wall and its lower border extended partially across the internal os of the cervix. Mother and baby survived. Note the anterior displacement of the head from the sacral promontory, a distance of 6.5 cm. on the film. The head is not only over-riding the symphysis pubis, but lies 3.5 cm. above it. This film presents a classic picture of low posterior wall placenta with partial previa.

Film B: M. C., Unit No. 31166, x-ray No. 25096, a 24-year-old gravida v, para iv, had a painless "sudden gush" of bright blood from the vagina when she was at term, following which the above film was taken. The x-ray diagnosis was "low posterior wall placenta, with marginal placenta previa." There was further bleeding the following day, and at vaginal examination the lower border of the placenta was palpated 2 cm. above the internal os on the posterior wall of the lower uterine segment. Immediate section was done, at which time the placental position was verified. Mother and baby survived. Note the anterior displacement of the head from the sacral promontory (5.5 cm. on the film), and the fact that the head, in contrast to Film A, lies directly upon the symphysis pubis. This plate is a typical representation of low posterior wall placenta with marginal previa, and since it was taken with the patient standing the head came down as close to the symphysis pubis as the intervening uterine wall thickness would allow.

hyperextension of the lumbar spine. We usually take standing cystograms in such cases, and occasionally have applied light manual pressure to the appropriate portion of the fetus, thus slightly augmenting the force of gravity in bringing the head down to some degree of approximation with the bladder. If the lower uterine segment is filled in part or in whole by the placenta, the head will remain displaced in some upward direction from the inlet of the pelvic canal as it did in Film A in both Figs. 2 and 3.

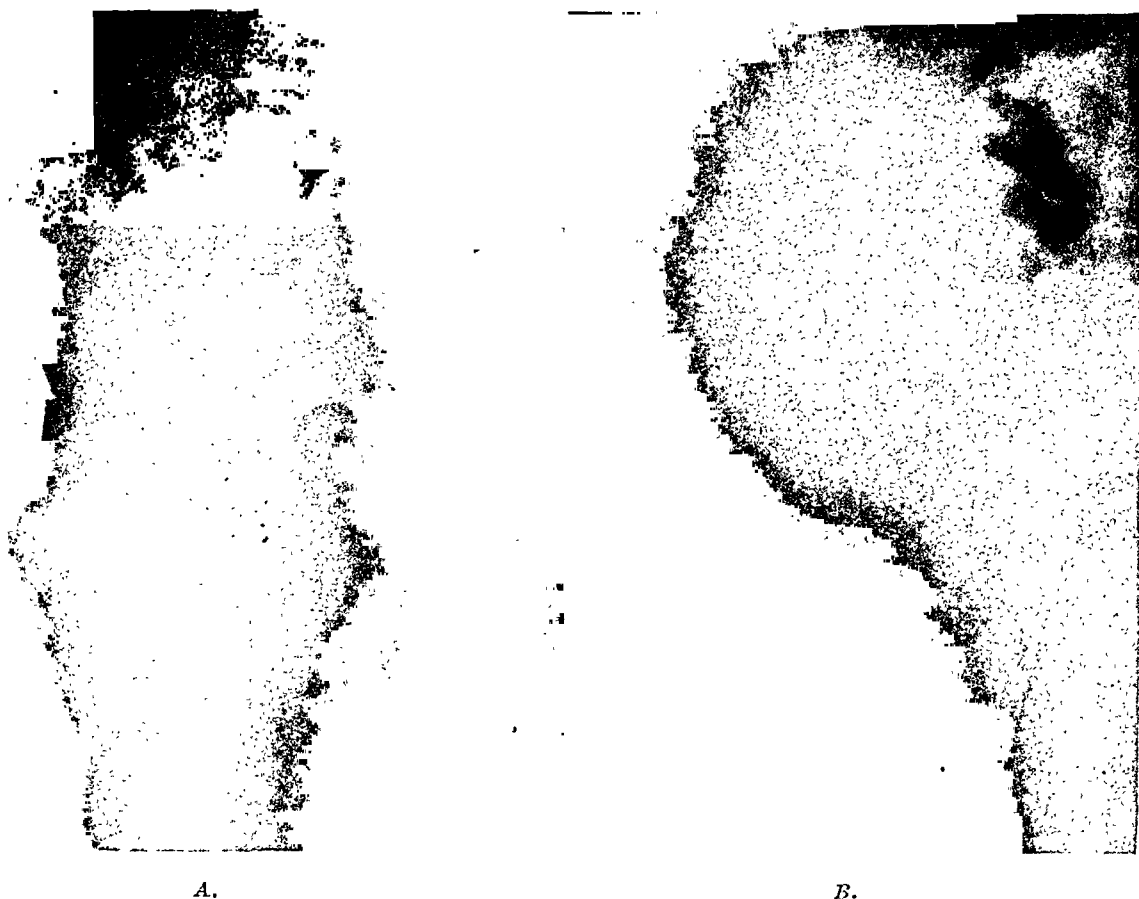


Fig. 2.—In the two above films the placenta lies low on the anterior uterine wall and they offer a comparison between partial and marginal placenta previa.

Film A: M. L., Unit No. 44225, X-ray No. 26248, a 28-year-old gravida ii, para i, had slight vaginal staining in her 21st, 23rd, and 25th weeks of pregnancy. In her 27th week she passed a small amount of bright blood and reported to the Out-Patient Department, where transverse lie of the fetus was discovered. X-ray studies were made, from which it was felt that she probably had placenta previa, with the placenta low-implanted on the anterior uterine wall. At the beginning of her 29th week she had a sudden vaginal hemorrhage, came to the hospital at once, and cystography was carried out (Film A). As this standing lateral cystogram shows, the head (outlined by arrows) is "riding" 6.5 cm. (on the film) above the bladder, and 9 cm. above the symphysis pubis. The x-ray diagnosis was "low-implanted anterior wall placenta, with partial previa," which was shortly confirmed at vaginal examination. Brisk bleeding occurred, and a Braxton Hicks version was done, a  $2\frac{1}{2}$ -pound infant, which succumbed, being shortly delivered. The mother survived without difficulty.

Film B: L. K., Unit No. 37826, X-ray No. 24995, a 32-year-old gravida iv, para iii, had vaginal bleeding with cramps in her 30th week of pregnancy, following which episode the above x-ray was taken. The roentgenologic diagnosis was "low implanted anterior wall placenta, with marginal or partial placenta previa." She had further bleeding at the beginning of her 34th week, following the onset of desultory bleeding, and vaginal examination revealed the lower placental border to lie about 1 cm. above the internal os on the anterior wall of the lower uterine segment. Classical section was done at once, at which time the position of the placenta was confirmed. Note the upward displacement of the head (6.5 cm. on the film) from the symphysis pubis, also its relatively normal relation to the sacral promontory (a distance of 2.5 cm.). The placenta is seen to lie over the entire length of the anterior uterine wall, and this film presents a classic picture of anterior wall marginal placenta previa.

We do cystographic studies in cases in which the placenta is not adequately demonstrated in the body or fundus of the uterus by the soft-tissue technique, or when the film suggests that a major portion of the placenta lies in the lower uterine segment, or if the head is displaced upward or to one side of its usual more or less central position in or above the inlet of the pelvic canal. Thus, if there are any findings suggestive of the presence of placenta previa, we do cystography. Our usual method is to inject 100 to 200 c.c. of 12.5 per cent sodium iodide solution into the bladder. We then take an anteroposterior film with the patient lying on her back. If this film is not conclusive, or if we appear to have a placenta lying low on the posterior or anterior wall, we turn



Fig. 3.—The two above films were taken on the same patient at an interval of six weeks. They show the persistent and similar displacement of the head which is frequently seen in cases of complete placenta previa.

C. S., Unit No. 26248, X-ray No. 25932, a 32-year-old gravida vii, para vi, had sudden, painless vaginal bleeding in her 26th week. She was admitted to the hospital and x-ray studies were made (Film A). As Film A shows, the left horn of the bladder is depressed lower than the right horn, and the head is displaced upward and to the right. A roentgenologic diagnosis of "low-implanted left lateral wall placenta, with complete placenta previa" was made. The patient was kept in the hospital, and another x-ray was taken at the beginning of her 32nd week (Film B). This second film shows the increased size of the fetus, and the head is similarly displaced, but is higher and more to the right, as one would naturally expect in view of its increased size. The soft tissue detail of the lower uterine segment, which appears to be filled by the placenta, is plainly visible in this film. The patient remained in the hospital, and when she was 6 weeks from term she had a sudden profuse painless hemorrhage. Section was done at once, the baby being so delivered 28 minutes following the onset of the bleeding. The placenta was found to lie exactly as pictured in the x-rays, and its lower border covered and extended 2 inches to the right beyond the internal os of the cervix. Mother and baby survived.

Film A was taken with the patient standing, and in such a case, where the head still does not settle down into the superior bladder concavity, one can be reasonably certain that it is displaced therefrom by some soft tissue mass which is occupying the lower part of the lower uterine segment. This case also illustrates the necessity of taking anteroposterior views of the uterus in order to visualize the occasional placenta implanted on a lateral uterine wall. The lateral films in this case did not show the placenta, and were of value only insofar as they thereby suggested a lateral wall implantation.

the patient on her side and take a lateral cystogram. If these two films are unsatisfactory, or if the presenting part is riding too high above the bladder, we will take anteroposterior (Film A, Fig. 3) and, if indicated, lateral views (Film A, Fig. 2) of the bladder with the patient standing. If the sigmoid is filled with feces and obscures the relationships of the lateral cystogram, we gently flush it out and put some air in it. This procedure is of particular value in cases where there is a low posterior wall placenta as the air-filled sigmoid allows greater definition of the posterior half of the lower uterine segment. It is very seldom that these measures will not allow one to rule in or out the presence of placenta previa, particularly if the duration of the pregnancy is thirty-four weeks or more.

The films are read and reported by the Resident Obstetrician. A small percentage of them are also taken by the Resident Staff, but most are taken by our regular technicians. Our x-ray department is on the delivery floor, and at any time, day or night, we can obtain x-ray studies on our patients within a few minutes. We believe that this is an ideal system, both in treating our patients and in training our Resident and House Staffs.

### Studies and Results

We have studied the films taken on 488 women for localization of the placenta during 1945, 1946, and 1947. Four hundred thirty-two of these were patients with uterine bleeding occurring in the third trimester. The other fifty-six cases were x-rayed because of persistent transverse or oblique position of the fetus in the last ten weeks of pregnancy. The 432 cases of bleeding occurred during a period in which there were 14,166 deliveries after viability. Hence 3.05 per cent of all patients had x-ray studies because of uterine bleeding.\*

In our series of 488 women who were x-rayed, the films on 14 did not allow our visualization of the placenta because the pregnancy was too early to allow adequate definition, because of the presence of twins or marked hydramnios, or as the result of technical error. Thus we finally had readable films on 474 women, and they constitute the series here reported.

In 414 cases, or 87.3 per cent, we were able to make the diagnosis, "negative for placenta previa," from the first soft-tissue films without difficulty, and in this group we cannot discover any evidence that we missed a single case of placenta previa. In the other 60 cases, or 12.7 per cent, we resorted to further films, cystograms, or more intensive study of the original plates because of obvious or suggestive evidences of placenta previa. The roentgenologic diagnoses resulting from our deliberations on the total series are represented in Table I. For the special purposes of this study all of the x-ray diagnoses presented in this table were made without knowledge of the actual clinical findings, and the only history known was the patient's parity, expected date of confinement, and the fact that she had had some bleeding (except in the films which showed transverse position of the fetus). All clinical findings were determined either at delivery, at sterile vaginal "double set-up" examination, or at cesarean section.

In our total series, we had 39 cases of placenta previa, complete previa being present in 21 women, partial previa in 8, and marginal previa in 10. Not included in our series are 10 additional cases of placenta previa which occurred during the period covered by this study. These patients, on arrival at the hospital, were bled out or in shock. Their condition was such that emergency transfusion, vaginal examination, and cesarean section were indicated, and we did not subject them to the loss of time that x-ray studies would have necessitated.

\*Our hospital records show that about 87.5 per cent of the cases of uterine bleeding in the third trimester had x-ray studies, and thus, by interpolation, we can derive a figure of about 3.18 per cent for the incidence of third trimester uterine bleeding in our clinic as a whole.

The most dangerous mistake one can make in diagnosing these films, obviously, is to say, in any given case, that the plate is "negative for placenta previa" when, in actual fact, the woman does have this condition. As Table I shows, we made this serious mistake in three cases. In each case, however, the degree of previa was only marginal. Table II shows an analysis of these cases.

TABLE I. ACCURACY OF ROENTGENOLOGIC DIAGNOSIS OF PRESENCE OR ABSENCE OF PLACENTA PREVIA IN A SERIES OF 474 CASES

	NUMBER OF CASES	CASES DIAGNOSED "NEGATIVE FOR PLACENTA PREVIA"		CASES DIAGNOSED "POSITIVE FOR PLACENTA PREVIA"	
		DIAGNOSIS CORRECT	DIAGNOSIS INCORRECT	DIAGNOSIS CORRECT	DIAGNOSIS INCORRECT
A. Cases readily diagnosed from first films*	414 or 87.3 per cent	414	none	none	none
B. Cases suggestive of placenta previa, and given further x-ray study and/or deliberations†	60 or 12.7 per cent	14	3	37	6
Totals		428	3	37	6
Diagnostic error		0.7 per cent		16.2 per cent	
Total correct diagnoses		465			
Total incorrect diagnoses		9			
Total diagnostic error		1.9 per cent			

\*No special clinical check-up was made as to the true location of the placenta in these cases, but at delivery there was nothing to suggest that some degree of placenta previa had been present.

†Actual position of placenta was determined in this group, either by sterile vaginal examination or at cesarean section.

As Table I shows, we made the incorrect positive diagnosis of placenta previa in six cases. While the false positive diagnoses constitute technical errors in the method itself, they are not potentially dangerous to the patient. Table III shows an analysis of these cases.

The obvious fact disclosed in Tables II and III is that we were able to diagnose complete, or central, placenta previa correctly in all of the 21 instances in which it occurred in our series of 474 cases. All of the eight women who had partial placenta previa also were correctly diagnosed. We made false negative diagnoses in three of the ten cases in which marginal placenta previa was present. No incorrect positive diagnoses for complete placenta previa were made, but we did make one for partial previa, and five for marginal previa.

In two of our three false negative diagnoses (see Table II) we underestimated how far down the lower border of the placenta extended on the posterior wall of the lower uterine segment, and this particular situation thus constituted, for practical purposes, our chief diagnostic pitfall.

In our six false positive diagnoses (see Table III) we overestimated how far the edge of the placenta extended downward when it was implanted low on the anterior wall in four of the cases, and we made the same error in two cases when it was low on the posterior wall.

We did not make any incorrect diagnoses from our cystogram films. In the cases in which we resorted to this technique, we confirmed the presence of placenta previa in 39 per cent, ruled it out in 50 per cent, and confirmed low implantation in 11 per cent. Cystographic studies were not done on any of the three cases represented in Table II, because in two of them (Cases 1 and 2) the clinical picture was obviously that of placenta previa until proved otherwise by sterile vaginal "double set-up" examination. These two cases required immediate emergency measures and there was neither the need nor the time for further



x-ray studies. In the third case in Table II (No. 3), cystography was not done because the patient had a second bout of bleeding one week following her first episode, and sterile vaginal examination was decided upon and carried out forthwith.

TABLE II. ANALYSIS OF THE 3 CASES OF MARGINAL PLACENTA PREVIA IN WHICH INCORRECT ROENTGENOLOGIC DIAGNOSIS WAS MADE

	NUMBER OF WEEKS PREGNANT AT TIME OF X-RAY	POSITION OF PLACENTA AS DIAGNOSED BY X-RAY	POSITION OF PLACENTA AS DETERMINED CLINICALLY	TYPE AND AMOUNT OF VAGINAL BLEEDING	TREATMENT	OUTCOME FOR MOTHER AND INFANT
M. S., X-ray No. 3,314; Unit Hist. No. 41,718	32	Low-im- planted on posterior uterine wall	Low-implanted on posterior uterine wall, with lower border $2\frac{1}{2}$ cm. above internal os when 2 cm. dilated	Sudden pain- less bleeding of 300 c.c. with subse- quent contin- uous trickle	Despite x-ray diagnosis, clinical pic- ture clearly indicated need of vaginal examination, which was done and fol- lowed by sec- tion	Both survived
E. B., X-ray No. 23,487; Unit Hist. No. 37,205	32	Low-im- planted on posterior, and partly on left lat- eral uterine wall. Ques- tionable marginal placenta previa	Low-implanted on posterior and left lat- eral uterine wall, lower border lying almost at internal os	Sudden pain- less bleeding of 400 c.c. with subse- quent contin- uous trickle	Despite x-ray diagnosis, patient's clin- ical condition clearly in- dicated need of section, which was done at once	Both survived
M. C., X-ray No. 24,760; Unit Hist. No. 42,925	$29\frac{1}{2}$	Low-im- planted on anterior uterine wall	Marginal pre- via, placenta low-implanted on anterior uterine wall	"Several sud- den gushes" at $29\frac{1}{2}$ weeks, followed by another sud- den flow at $30\frac{1}{2}$ weeks	Vaginal exam- ination done at $30\frac{1}{2}$ weeks, and No. 5 bag inserted. Normal spon- taneous deliv- ery resulted	Mother survived. Infant weighed 2 pounds 12 ounces at birth, died of pre- maturity

As far as the outcome was concerned in the nine cases we diagnosed incorrectly, all of the mothers survived and there was no avoidable fetal mortality. Our x-ray diagnoses, as to placental position, were correct in 98.1 per cent of the 474 cases, which is practically the same rate as was achieved by Buxton et al.<sup>24</sup> and by Bishop.<sup>10</sup> If we count the previously mentioned unreadable films taken on fourteen women as diagnostic failures, our method in the total series of 488 cases achieves a correctness of 95.3 per cent.

As has been stated, only 432 of the women in our series were x-rayed because of vaginal bleeding. The other 56 cases had routine x-ray studies solely because of the discovery, during routine palpation in the Out-patient Department, of persistent transverse or oblique position of the fetus in the last ten weeks of pregnancy. We have followed this practice at the Boston Lying-in Hospital for several years, and have found that transverse position of the fetus has been noted clinically, or by x-ray, in about one-third of our cases of placenta previa. Such fetal position, thus, is a particularly important diagnostic sign in placenta previa.<sup>30</sup>

Of the 56 patients in our series who had transverse or oblique position of the fetus, 12, or 21.4 per cent, had placenta previa. Breech presentation was found in 53 women, and, of these, three had placenta previa, all of which conditions were correctly diagnosed by x-ray. Three hundred sixty-seven cases had cephalic presentation, in twenty-four of which there was placenta previa. Two of the incorrect negative diagnoses for placenta previa (Cases 1 and 2, Table II) were made in women with cephalic presentation, while the third (Case 3, Table II) was made in a woman who had transverse position of the fetus at the time the film was taken.

TABLE III. ANALYSIS OF 6 CASES INCORRECTLY DIAGNOSED AS HAVING PLACENTA PREVIA

	NUMBER OF WEEKS PREGNANT AT TIME OF X-RAY	POSITION OF PLACENTA AS DIAGNOSED BY X-RAY	POSITION OF PLACENTA AS DETERMINED CLINICALLY	TYPE AND AMOUNT OF VAGINAL BLEEDING	TREATMENT	OUTCOME FOR MOTHER AND INFANT
1. H. P., X-ray No. 21,047; Unit Hist. No. 39,676	40	Low— implanted on posterior wall, with marginal previa	Character of labor and delivery excluded previa	Slight spotting	Spontaneous onset of labor. Nor- mal low forceps delivery	Both sur- vived
2. P. E., X-ray No. 23,045; Unit Hist. No. 16,565	33½	Marginal or partial previa, placenta low on posterior wall	Vaginal exami- nation done, no placenta previa found	Slight spotting at 22 weeks, at 33½ weeks, and at 35 weeks	Spontaneous onset of labor, with low forceps de- livery at 35½ weeks	Both sur- vived
3. C. C., X-ray No. 23,337; Unit Hist. No. 23,063	31½	Low— implanted on anterior uterine wall, with marginal previa	Normal char- acter of labor and delivery excluded previa	None. X-rays taken because of persistent transverse position of fetus	Spontaneous cor- rection of fetal position to cep- halic presentation occurred. Nor- mal spontaneous delivery at term	Both sur- vived
4. E. S., X-ray No. 23,486; Unit Hist. No. 10,560	27½	Low— implanted on anterior uterine wall, with marginal previa	Low— implanted on anterior wall, but not a marginal previa	Moderate bleeding off and on for 3 days (had anemia and Grade I pre- eclampsia)	Uterus tense and tender. Clinical picture was that of partial pre- mature toxic sep- aration of pla- centa. No previa found at vaginal examination. Sec- tion done	Mother sur- vived. In- fant's birth weight, 2 pounds, 8 ounces. Died of prema- turity
5. G. E., X-ray No. 24,147; Unit Hist. No. 8,000	30	Low— implanted on anterior wall, with marginal previa	Normal char- acter of labor and delivery excluded previa	None. X-rays taken because of persistent transverse position of fetus	Spontaneous onset of labor, with normal spontane- ous delivery at term	Both sur- vived
6. G. L., X-ray No. 24,425; Unit Hist. No. 18,543	34	Low— implanted on anterior wall, with marginal previa	Normal char- acter of labor and delivery excluded previa	Very slight spotting at 34 weeks	Spontaneous onset of labor, with normal spontane- ous delivery at term	Both sur- vived

### Discussion

The figures denoting the accuracy of x-ray localization of the placenta generally have been impressive. In this paper, they turned out to be far better than we had expected when the study was in progress. We were certainly not sure of our diagnosis in quite a few of the cases, but this feeling has been some-

what allayed by the fact that we subsequently were proved to have been correct in 98 per cent of the instances. It is difficult to feel sure of a diagnosis when one is making it largely on negative instead of positive evidence, as is usually the case in this work. The reading of soft-tissue films of the pregnant uterus is in a different category from reading a plate showing a fractured femur. In the case of the fracture, one is able to make a straightforward *diagnosis* on positive evidence. It is quite the opposite with soft-tissue films of pregnancy, for in them one is merely able to cite an *impression* or an opinion as to where the placenta lies.

We have encountered many pitfalls, as have others,<sup>18, 21, 24</sup> in interpreting our films. In a first film, we have found the head riding high above the inlet and over-riding the symphysis in cases in which the patient merely had a bladder full of urine. In these instances we have had the patient empty her bladder, have injected it with about 100 c.c. of sodium iodide solution, and have taken a lateral standing cystogram. A rectosigmoid full of soft feces can produce much the same picture.

In the multigravid patient with marked relaxation of the anterior abdominal wall, there can be some anterior and upward "floating" of the head away from the pelvic inlet when she lies on her side on the x-ray table.<sup>30</sup> In such a case, a standing lateral film, with, if necessary, some light manual pressure exerted downward on the upper fetal pole, usually brings the presenting part down to a position in which it "rests on the bottom" of the lower uterine segment, and the true anatomic situation then can be correctly pictured.

The localization of the placenta in twin pregnancies is difficult, and, in our series, in the several instances in which this condition was encountered, we were not able to visualize it definitely. The same was true in cases with marked hydramnios and in normal pregnancies of a duration of less than 27 weeks. The delineation of the placenta is much more accurate and reliable in pregnancies of 32 or more weeks, and this is particularly true in cystography. It is unusual for a cystogram to be as accurate at 26 weeks of pregnancy as that pictured (Film A) in Fig. 3, and in any case earlier than 32 weeks cystography is best done with the patient standing. Nonobservance of this rule may give a misleading representation of the actual anatomic relationships. If the anteroposterior film is not conclusive, a lateral cystogram also should be taken.

It is difficult to demonstrate exactly what benefit our clinic has derived from the adjunct diagnostic aid this x-ray technique has given us. We can state, however, that in a recent sampling series of 56 cases of placenta previa we had no maternal mortality, and that 21 per cent of those cases that had complete previa (they had transverse position of the fetus) were diagnosed by x-ray and had cesarean section before any vaginal bleeding had occurred. Seventy per cent of the infants in this sampling series survived, 14 per cent were stillborn, neonatal death occurred in 14 per cent (chiefly from prematurity), and 2 per cent were nonviable.

At every prenatal visit, each patient is specifically asked if she has had any vaginal staining or bleeding. If she answers in the affirmative and is at or beyond her 26th to 28th week of pregnancy, routine soft-tissue x-ray studies are

made. If we feel relatively certain, from our study of the films, that there is no placenta previa present, we send the patient home with whatever instructions are indicated. It is a relief to us not to have to admit such a case of slight vaginal staining to the hospital for a period of observation, and it is also a financial saving for her. Furthermore, we do not thus tie up any of our beds in such needless fashion, and we are able to rest secure in our minds that she has no more than 1 chance in 50 of having placenta previa. By the same token if the x-rays are positive for placenta previa, we keep her in the hospital and permit her to approach fetal viability as nearly as her clinical course, with safety to her, will allow us (see case report under Fig. 3).

Our method also gives us a rapid and simple means, in cases of third trimester bleeding, of differentiating between placenta previa and partial premature separation of a normally implanted placenta. Once this point is settled we can proceed with the indicated course of treatment.

We do not intend, in any wise, to convey the impression that x-ray studies of the placental position should supplant vaginal examination in the diagnosis of placenta previa. Our experience has taught us, however, that the foreknowledge supplied by our x-ray studies has undoubtedly helped us to avoid an appreciable degree of hemorrhage following vaginal examination, when such examination has been made with a mental picture of the apparent position of the placenta already in mind.

X-ray localization of the placenta, as a routine in our hospital, has been successfully carried out over a continuous period of several years, chiefly because of the genuine interest of the Visiting and Resident Staffs in the method. They have maintained this interest because the method has served them well. In view of the facts that special or inordinately expensive x-ray equipment is not necessary, that any technician and members of the Resident Staff can be taught to take the films, and that a Resident Obstetrician can be taught to read the films, we feel that this method is practical for use in many hospitals in which it is not now being employed. If a careful and conscientious attitude is exercised by the technician taking the films and the doctors who read them, they will be much gratified by the long-range beneficial results it is possible to attain.

### Conclusions

1. The history of the development of the methods of x-ray visualization has been traced.
2. The x-ray technique employed at the Boston Lying-in Hospital has been described, and our routine methods of securing the various x-ray views of the pregnant uterus in the last trimester have been outlined in detail. The chief objective, we have found, is to position the patient in such fashion that an edge-wise view of the central vertical axis of the placenta will be represented on the film.
3. Our method of taking x-ray cystograms has been described, and the indications for so doing have been stated.
4. We were unable to visualize the placenta in the x-ray films of fourteen women in our total series of 488 cases, but even though we counted these failures

of method in with our diagnostic failures, we still achieved a correctness of 95.3 per cent in localization of the placenta insofar as ruling in or out placenta previa is concerned. In the series of 474 cases in which the placenta was visualized, we made the correct diagnosis of presence or absence of placenta previa in 98.1 per cent.

5. There were 39 cases of placenta previa in our series, and we diagnosed all of these correctly except in three instances in which marginal placenta previa was present. This gave us a correct diagnostic achievement of 100 per cent in complete previa (21 cases), of 100 per cent in partial previa (8 cases), and of 70 per cent in marginal previa (10 cases). This demonstrates that accuracy in the differential x-ray diagnosis between marginal placenta previa and low-implanted placenta was, in our hands, difficult to attain. No maternal mortality, and no increase in fetal or neonatal mortality resulted from our three "false negative" diagnostic errors.

6. We made no incorrect diagnoses in cases in which cystography was done. We were not able to do cystographic studies in the three cases of diagnostic failure for reasons which we have explained. In doubtful cases, we have achieved good results by obtaining both anteroposterior and lateral cystograms of the patient when in standing position.

7. We have had difficulty in visualizing the placenta in cases of twins, marked hydramnios, and in normal pregnancies of a duration of less than 27 weeks.

8. We have presented, as evidence of the beneficial diagnostic aid this x-ray technique has given us, the fact that in a recent sampling series of 56 cases of placenta previa we have had no maternal mortality, and that 21 per cent of the cases of complete previa were diagnosed and treated before any vaginal bleeding had occurred.

9. Since special x-ray equipment is not necessary in carrying out these studies, since the x-ray technique is simple, and since the Resident Obstetrician or any interested roentgenologist can learn to read the films, we believe that this method is a useful aid in the diagnosis of the cause of uterine bleeding in the latter weeks of pregnancy.

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1512 ST. ANTOINE STREET

## SADDLE BLOCK ANESTHESIA\*

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**I**N THE past two years saddle block anesthesia in obstetrics has gained widespread popularity. Numerous articles have appeared in the recent literature and all are enthusiastic about its use. Our preliminary report was made in 1947.<sup>1</sup> It seems appropriate, therefore, to review our two years' experience and make a final report regarding the suitability of this anesthetic procedure in obstetrical cases.

### Material Studied

Since Sept. 6, 1946, heavy Nupercaine saddle block anesthesia† has been used in more than 1,200 selected cases delivered on the obstetrical teaching service of the Stritch School of Medicine, Loyola University. This service includes the Lewis Memorial Maternity Hospital, Mercy Hospital, St. Vincent's Infant and Maternity Hospital, and Misericordia Hospital. For the sake of uniformity of analyses, only the 877 cases delivered at the Lewis Memorial Maternity Hospital will be presented.

The pharmacology of "heavy nupercaine," the technique of administration, and the contraindications for this procedure have been mentioned in our previous report and need not be reiterated. The time of administration was the late first stage or the early second stage of labor. The dosage for most cases was 2.5 mg. and was repeated in only 36 cases, or 4 per cent.

### Results

The success of the procedure was based solely on the degree of subjective relief obtained by the mother and not on the level of anesthesia. Thus, we have classed as "incompletely relieved" those patients in whom saddle block anesthesia was present, but in whom some pain was perceived; and as "failures" those patients claiming "no relief," even though sufficient perineal anesthesia was present to permit episiorraphy.

In Fig. 1 the results of the 877 cases are depicted graphically. Eight hundred sixteen, or 93 per cent, of the mothers had complete subjective relief for over one hour; 53, or 6 per cent, obtained incomplete subjective relief, and eight, or 1 per cent, were classed as failures.

As may be seen from Fig. 2, 754 patients, or 86 per cent, of the 877 were delivered solely under the effect of saddle block anesthesia; 38 of these cases, however, were patients with "incomplete relief." The degree of analgesia was sufficient to permit delivery without the patient's requesting supplementary anesthesia.

\*Read before the Fifty-Ninth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons at Hot Springs, Virginia, Sept. 9, 10, and 11, 1948.

†Heavy Nupercaine Solution was supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

Supplementary delivery anesthetic was used in 123 patients, or 14 per cent. The two most important indications for this procedure were (1) to supplement waning spinal effect in patients delivering later than one and one-half to two hours after the administration of the nupercaine solution; and (2) to provide deeper anesthesia prophylactically for such operative procedures as forceps rotation (particularly Seanzoni maneuver), midforceps delivery, breech decomposition and extraction, version and extraction, etc. As has been pointed out previously, this latter is in keeping with the observation of Malpas of Liverpool that "under spinal anesthesia, the myometrium of the pregnant uterus exhibits heightened reactivity to various stimuli." The third reason for the supplementary delivery anesthetic was for psychological purpose. Light inhalation anesthetic was given to allay the fear and apprehension associated by some patients with the obstetrical procedures. These patients wished to be asleep at the time of delivery.

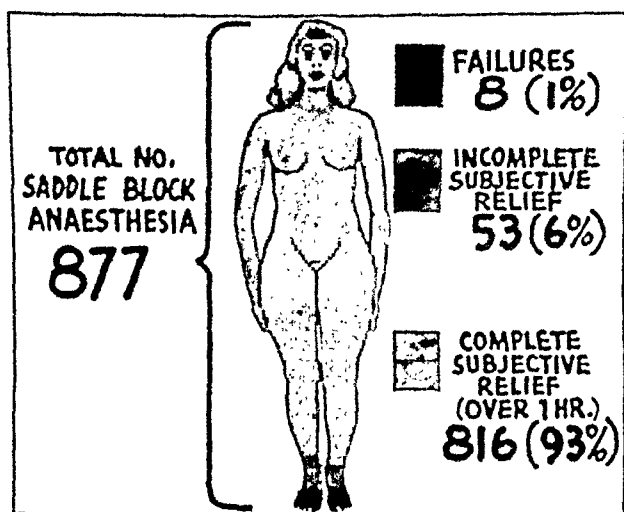


Fig. 1.

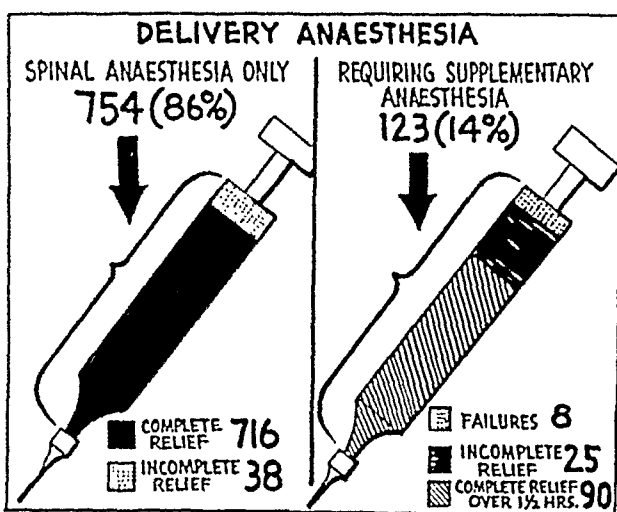


Fig. 2.

In two of the eight cases listed as failures, perineal anesthesia sufficient to permit episiotomy and episiorrhaphy was present, but as the patients stated they had had "no subjective relief" from labor pain, these could not be included in the "incomplete relief" group.

The duration of subjective relief varied from one hour to five hours, but the average was one to two hours. In general, prolonged relief was looked upon with suspicion as possible interference with the progress of labor. Our aim was to administer saddle block anesthesia when delivery was expected to occur within the following two hours.

The objective anesthetic effect, particularly on the perineum, generally exceeded three hours. An extreme of ten hours in one and seven hours and twenty-two minutes in another were noted in two cases early in the series. In these two cases, the perineal anesthesia was sufficient to permit episiorrhaphy.

The manner of deliveries is shown in Fig. 3. In our practice, the use of "prophylactic outlet forceps" is routine, and this type of delivery constitutes the major part of our cases. That a patient with complete subjective relief can be delivered spontaneously solely under the effect of saddle block anesthesia is shown by the 78 cases so delivered. Spontaneous deliveries could replace outlet forceps deliveries by having the patient "bear down" at the time of uterine contractions. Since the contractions are painless, the onset of uterine contraction must be detected by the patient's own hand on the abdomen, or by the ob-



stetrician, so that the accessory delivery forces may be synchronized with the expulsive force of the uterine muscles.

Condition of the infants at birth is shown in Fig. 4. There were 44 infants with birth weights under 5 pounds, 10 ounces, and these were arbitrarily grouped as "prematures." Unfortunately, the fate of these premature infants

TYPES OF DELIVERY		
Spinal only ↓ 716 - Complete Relief - 89 Suppl. Anaes. ↓		
78	SPONTANEOUS	6
494	OUTLET FORCEPS	37
97	LOW FORCEPS	19
14	MANUAL ROTAT'N, LOW FORCEPS	4
13	LOW FORCEPS ROTAT'N (EXTRACT'N)	8
2	MANUAL ROTAT'N, MID FORCEPS	0
1	MID FORCEPS ROTATION (Including Scanzoni maneuvers)	2
9	BREECH EXTRACTION	8
0	VERSION, EXTRACTION ON MRT	1
4	TWINS	4
38 - Incomplete Relief - 26		
7	SPONTANEOUS	4
23	OUTLET FORCEPS	12
3	LOW FORCEPS	6
4	MANUAL ROTAT'N, LOW FORCEPS	1
0	LOW FORCEPS ROTATION	1
1	BREECH	1
0	TWINS	1
0 - Failures - 8		

Fig. 3.

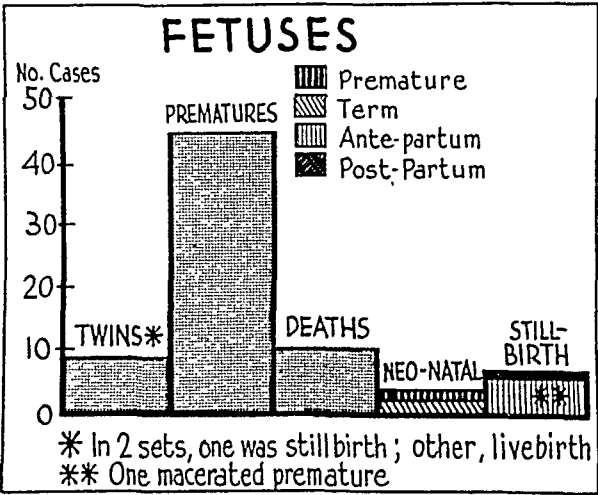


Fig. 4.

cannot be evaluated as the Chicago Board of Health Rules, set up by the American Committee on Maternal Welfare, required their transfer to hospitals with facilities for the care of prematures. There were four neo-natal deaths, and prematurity was the cause in two cases. Of the term infants, one infant weighed 10 pounds, 1/2 ounce at birth and was delivered in good condition as an "assisted breech" under supplementary ether anesthesia, but died two days later. Autopsy showed only cerebral edema and atelectasis. The second term infant weighed

6 pounds, 12 ounces at birth and was in good condition, but died twenty-four hours later. Of the six stillbirths, two occurred in two sets of twins. In each set one of the twins was macerated. Another of the stillbirths was a macerated premature infant weighing 4 pounds, 3 ounces.

The weight of the "prematures" is shown on Fig. 5.

TABLE I

UNTOWARD EFFECTS		
	NO. CASES	PCT
Untoward weakness (Slight to complete paralysis).....	869	100%
Effect on Blood Pressure		
Drop less than 20 mm. Hg .....	721	
" more " " " " .....	156	18%
Spinal Reaction (?sensitivity to drug)	1	
Post spinal headaches.....	125	14%
Neurological complications: Foot drop	1	

Table I lists the untoward effects of saddle block anesthesia. Motor weakness was present in 100 per cent of cases listed as completely or incompletely relieved. The degree of motor palsy varied from mild weakness to complete paralysis of the legs. These were all transient and caused no inconveniences. Significant drop in blood pressure of more than 20 mm. was noted in 156 patients, or 18 per cent, but in only 77 did the systolic pressure fall below 100 mm. level. In nine cases the pressure dropped below 80 mm. All, however, responded readily to ephedrine and oxygen therapy. There was one case which we considered a "spinal reaction" and attributed to drug sensitivity. This case has been reviewed in our preliminary report. The neurologic complication of foot drop was also reported previously. Recovery from this complication was spontaneous and complete by the tenth postpartum day.

An analysis of cases with blood pressure fall below 100 mm. systolic pressure is shown in Fig. 6.

Postspinal headache occurred in 14 per cent of the cases and the day of occurrence is shown on Fig. 7. This undesirable side effect continues to present a big problem. The cause of these headaches is as yet unknown. That it is not specifically caused by Nupercaine solution is indicated by the occurrence of identical headache following diagnostic spinal fluid aspiration. Furthermore, the 19.5 per cent incidence of headache with heavy Pontocaine spinal anesthesia reported by Ahearn and Huston,<sup>2</sup> and 14.5 per cent incidence reported by Dieckmann and his associates<sup>3</sup> with Metycaine, Novocain, and Pontocaine, as well as Nupercaine, suggest that the headache is not specific to the agent used.

Our attempt at prophylaxis with ephedrine administration, minimization of spinal fluid loss at the time of spinal puncture, and early assumption of upright position from the day of delivery have not reduced the incidence of post-spinal headache. Characteristically, the headache is aggravated by upright position and relieved by lying down, but we have not kept any patient flat in bed for six to seven days in an attempted prophylaxis against developing post-spinal headache.

Therapeutically, we have tried ephedrine, antihistaminic substances, 500 c.c. of 20 per cent glucose intravenously, caffeine, etc., as well as the usual analgesics, without consistent results. We are still seeking an effective prophylactic or therapeutic agent.

There have been five instances of retained placenta. We do not believe the use of saddle block anesthesia contributed in any way to this retention.

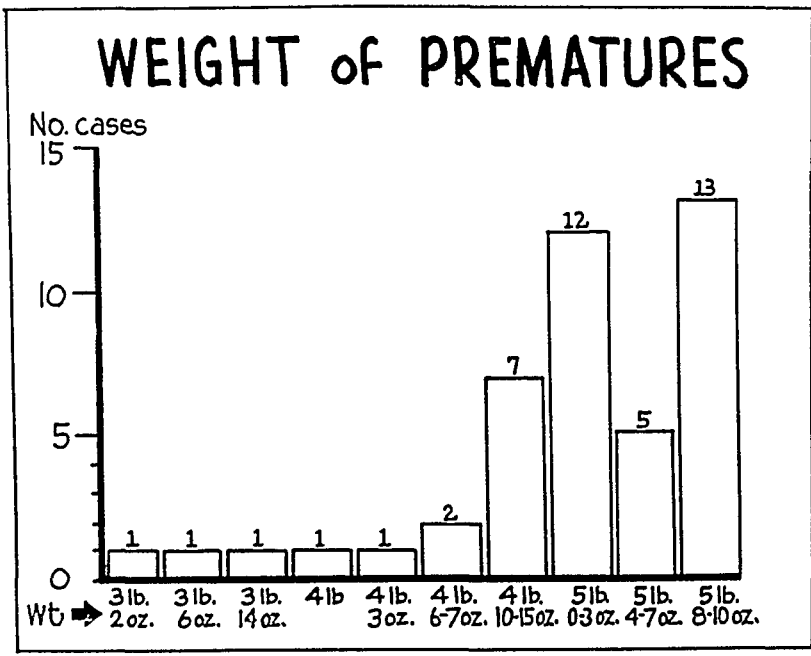


Fig. 5.

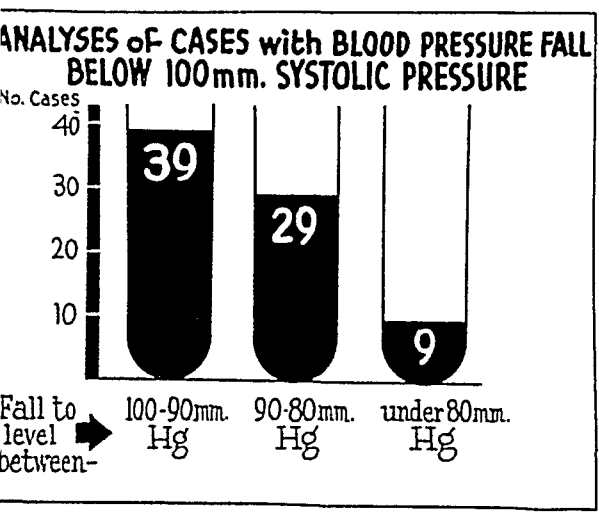


Fig. 6.

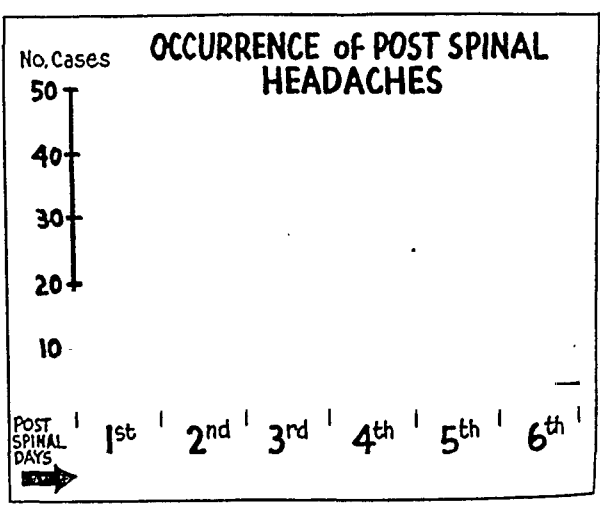


Fig. 7.

Discussion

Saddle block anesthesia has a very definite place in obstetrics, particularly in the second stage of labor. It should not, however, be used to the exclusion of all other forms of analgesic-anesthetic agent. The ideal obstetrical analgesic

agent is the one which will provide absolute safety for both the fetus and mother, complete subjective comfort for the mother, noninterference with the progress of labor, complete absence of undesirable side effect, simplicity and ease of administration, and facilitate the care of obstetrical patients. Saddle block anesthesia is not the ideal method, but is at present closest to this ideal. Spinal anesthesia is potentially dangerous, and hence should not be used by the inexperienced physician nor by an obstetrician who will not take cognizance of the potential danger and exercise all precautions.

Neurological complication, although rare, is always potentially present, as pointed out by Nicholson and Eversole,<sup>4</sup> and was illustrated by our case with foot drop noted on attempted ambulation on the third postpartum day. Trauma to the nerve or cord may be suggested by radiating pain or bloody tap. A previously anesthetized nerve or cord is not capable of causing radiating pain. This is one of the most important reasons for our reluctance to repeat the spinal injection in a patient where some anesthesia is present. Impurities, deterioration, and contamination are the other causes of neurologic complication.

Postspinal headaches may be severe enough to cause worry to the physician. There have been a few instances of severe headaches accompanied by neck stiffness to suggest meningismus. These headaches justify the attitude of some patients in refusing this form of analgesia. The 14 per cent incidence of postspinal headache is too high and too disturbing to label saddle block anesthesia, with the present available agents, as the ideal obstetrical agent.

Other manifestations demanding utmost care and precaution are the drug sensitivity and the effect on the blood pressure. Drug sensitivity may threaten the life of the mother and baby and needs no elaboration. The fall in blood pressure, however, may be disregarded by the inexperienced physician, and hence needs emphasis. Hingson et al.<sup>5</sup> have pointed out that with maternal pressure remaining below 80 mm. Hg systolic, fetal anoxia may be demonstrable in every case where this condition is allowed to exist for five minutes or longer. He believes that the pressure due to resting and contracting uterine tone is greater than the arterial pressure (of below 80 mm. Hg). Failure to prevent or treat promptly the fall in blood pressure may result in irreparable damage to the fetus. *A live child does not signify an undamaged brain.* The anesthetist is responsible for the preventable cerebral damage even when such manifestation occurs later in life.

We have dwelt at length on the danger of spinal anesthesia to emphasize the need of proper precaution. To a qualified anesthetist-obstetrician this method of obstetrical analgesia has been most nearly ideal. Careful evaluation and selection of the patient, exercise of proper precaution (such as testing for drug sensitivity, etc.) and the use of single-dose method (given at the optimum time) have minimized the danger both to the mother and the fetus. Our routine is as follows:

1. Selection of the patient. Absence of contraindications, such as cerebrospinal disease, pyogenic infection at or adjacent to the site of puncture, poor condition of the patient (shock, coma, sepsis, severe hypotension, etc.) obstetrical complication, hypersensitivity to the drug and unfavorable type of patient (neurotic type, those suffering with chronic backache, headache, or migraine).

2. Skin testing for sensitivity.

3. Administration at late first stage or early second stage of labor, when delivery is thought to occur within the following two hours.

4. Observation of all precautionary measures:

- a. Barbiturates to counteract possible spinal reaction (particularly where cocaine derivatives are used; Nupercaine is a quinoline derivative).

b. The routine use of ephedrine prior to administration of spinal anesthetic agent partly to guard against preventable fall in blood pressure, and partly as prophylaxis against allergic manifestations, of which postspinal headache may be one.

c. The administration of oxygen in all cases of fetal bradycardia together with the prompt effective treatment of maternal hypotension.

The first two points in our routine are obvious. The selection of time of administration requires elaboration. We have satisfactorily controlled the discomfort of the first stage of labor with effective use of such drugs as morphine, morphine-scopolamine, Demerol, Demerol-scopolamine, barbiturates, and barbiturates in combination with morphine, Demerol, scopolamine, etc. The saddle block anesthesia is reserved for the late first stage or early second stage of labor. Too early administration may impede the progress of labor or necessitate either a repeat injection of the spinal anesthetic agent with all of its concomitant dangers enumerated above, or else resort to other forms of delivery anesthetics. In the latter event, the beneficial advantages of spinal anesthesia is nil and the potential danger too great to justify its use.

We believe the routine use of ephedrine prior to the spinal administration is a wise precaution against preventable blood pressure fall and possible allergic drug reaction. In our preliminary report, ephedrine was only used as dictated by the fall in blood pressure and not prophylactically. In the 67 cases of blood pressure fall exceeding 20 mm. Hg reported in that series, only 13, or 20 per cent required use of ephedrine to restore the pressure to normal range.

There are many advantages of properly used saddle block anesthesia. For the fetus, spinal anesthesia provides maximum protection from two standpoints; (1) pharmacologically, the toxic drug reaction and depression to the baby are absent; (2) mechanically, the trauma to the fetal head is minimized by the elimination of involuntary "bearing down" reflex. The importance of this protection has been emphasized by Masters<sup>6</sup> of George Washington University School of Medicine in the delivery of premature infants.

For the laboring mother, successful saddle block anesthesia provides absolute comfort almost immediately. Due to this comfort the laboring mother is able to take adequate nourishment and fluids and to obtain rest. Furthermore, the presenting part is brought to the outlet by the action of uterine contraction alone, hence the appearance of the presenting part at the outlet indicates complete dilatation and retraction upward of the cervix. The importance of complete retraction of the cervix has been adequately emphasized by Dr. Calkins<sup>7</sup> and needs no comment here.

From the nursing staff's standpoint, the care of the patient is made easier. Only minimum equipment is required, and the perfectly clear mind of the patient makes nursing care simple. Due to the nature of the anesthesia, "last minute" confusion and excitement of imminent delivery are eliminated.

From the obstetrician's standpoint, the advantages are many. It is the anesthetic of choice in cardiac patients, as well as in patients suffering from respiratory diseases. The danger of the complication of aspiration, and the additional narcotizing effect of supplementary delivery anesthesia in patients given heavy predelivery sedation is eliminated. The simplicity of administration makes its use available to all.

The increased incidence of operative deliveries has been cited as a disadvantage. The use of saddle block as a terminal procedure will eliminate most of this objection, as rotation will occur usually before the late first stage or early second stage. That the number of spontaneous deliveries can be increased by utilization of the accessory muscle of expulsion synchronized with uterine contraction has been discussed already. Dieckmann and his associates,<sup>3</sup> in their

series of 719 cases, have also noted no significant increase of operative deliveries. They believe that the late institution of saddle block anesthesia is a factor in producing their low operative incidence.

### Summary

Eight hundred seventy-seven attempts at saddle block anesthesia with heavy Nupercaine solution have been analyzed. It provided complete subjective relief of at least one hour's duration in 816 cases, or 93 per cent, and incomplete subjective relief in 53 cases, or 6 per cent. Seven hundred fifty-four patients, or 86 per cent, were delivered under the sole analgesic effect of saddle block anesthesia. In 123 other patients supplementary delivery anesthetic was used to supplement waning spinal effect, for deeper anesthetic to permit operative maneuver and for psychological reasons only. Subjective relief was of one to two hours' duration on the average, but the perineal anesthesia usually exceeded three to four hours' duration. The time of administration was the late first stage or early second stage of labor. The incidence of operative deliveries was found to be low. The untoward effects found were 100 per cent motor weakness, 18 per cent incidence of blood pressure fall exceeding 80 mm. Hg, 14 per cent incidence of postspinal headaches, and a case each illustrating "spinal reaction" and "neurologic complication" (foot drop). There were ten dead babies, of which six were stillbirths and four neonatal deaths. Two neonatal deaths were due to prematurity.

### Conclusion

Saddle block anesthesia is the most nearly ideal for obstetrical analgesia and anesthesia if used judiciously by an experienced obstetrician. The maximum safety to the fetus and mother, the dramatic relief of the discomfort of labor and the simplicity of the technique make it attractive for the mother, the nursing staff, and the attending obstetrician. That there are certain potential dangers to the use of this type of anesthesia must be borne in mind at all times. Protracted or permanent neurologic complication may follow spinal anesthesia as well as general anesthesia. Drug reaction may endanger the fetus and the mother. It is, therefore, imperative that the most careful technique be meticulously observed and all precautions taken to guard against any danger. An experienced, qualified obstetrician can minimize the factors contributing to the potential danger. For such individuals, saddle block anesthesia provides the most nearly ideal form of obstetrical analgesic.

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## Discussion

DR. JAMES R. BLOSS, Huntington, West Va.—In our own service, which is an entirely private patient one, spinal anesthesia has been practically the only type employed for the past two years.

Metycaine in Ringer's solution has been the drug used. We have been somewhat hesitant about using the hyperbaric solutions and endeavoring to secure the "saddle block." Probably this hesitance has been due to the fact that the results thus far secured have been so satisfactory, in our experience.

It has seemed to us that the very prompt anesthetic effects of metycaine, and the absence of alarming falls in blood pressure, with evidences of the toxic symptoms noted at times when other agents have been employed, make this the more desirable agent.

We do not administer the spinal anesthetic until it is felt that delivery will be effected promptly, usually within an hour. It has appealed to us that more careful attention to analgesia during the first and early second stages has much to do with the successful outcome of the spinal anesthesia. In our experience the intravenous administration of demerol and scopolamine, with a barbiturate given by mouth has proved safe and successful for this purpose.

I am in agreement with Dr. Schmitz that in the hands of an experienced and qualified obstetrician who meticulously observes the most careful technique and takes all precautions to guard against possible but unpredictable complications, such as rapid and extreme fall in blood pressure, etc., this form of obstetric anesthesia provides the most nearly ideal at the present time.

One cannot refrain from re-emphasizing the precautions to be observed and the adherence to a definite routine. We must realize that this procedure is potentially dangerous and that many untoward sequelae may result. This is true of all agents used for obstetric anesthesia when carelessly administered. When carefully administered by qualified obstetricians, the outstanding advantages, to both mother and infant, of this technique for the relief of pain for women in labor justify its employment.

DR. RUSSELL J. MOE, Duluth, Minn.—The results of our experience with saddle block anesthesia in obstetrics using a hyperbaric Nupercaine solution coincide very closely with those reported by Dr. Schmitz. We have found it to be a safe and effective anesthetic agent for delivery.

That there is a need for a safer anesthetic to replace inhalation anesthetics in certain obstetric cases is indicated by a study of maternal deaths due to aspiration pneumonia. A recent one-year maternal mortality study in Minnesota, in which 112 maternal deaths were analyzed, revealed three maternal deaths due to aspiration secondary to an inhalation anesthetic.

In our early experience with Nupercaine saddle block we found it necessary to repeat the puncture in 24.4 per cent of the cases. This was due to the fact that the initial dose was administered too early in the course of labor, particularly in primigravidas.

As a result of too early administration and the necessity of repeat punctures, two facts soon became obvious. First, rotation of the presenting part was necessary in 31 per cent of the cases, and in only one of these was manual rotation possible. The increased irritability of the uterine muscles under saddle block anesthesia makes manual rotation more difficult. However, since using a single intrathecal injection after complete dilatation, the number of necessary rotations has decreased to 6 per cent.

Second, it became apparent that there was an increased incidence of postspinal headaches in the group that had multiple punctures. The single injection group had an incidence of 19 per cent headaches as compared with the essayist's 14 per cent, whereas the multiple injection group had an incidence of 35 per cent. The postspinal puncture headache is a distressing but not a serious complication. We now have two patients who complained of spinal puncture headaches, one of which was classified as severe, who have had subsequent deliveries under spinal anesthesia without headaches.

DR. SAMUEL A. COSGROVE, Jersey City, N. J.—I think it might be well if Dr. Schmitz, in closing the discussion, took pains to offer a definition of exactly what he means by "saddle block." Because, while it is, as several of the discussers have indicated, merely a fanciful name for a low single-shot spinal anesthesia, the term should properly be restricted to that type of low spinal anesthesia which employs a particular agent which assures a more lasting effect than is possible with other agents. It would seem to me that Dr. Bloss is talking about an entirely different procedure when he insists that his Metycaine solution be used within an hour of the delivery of the patient. Now, unless saddle block is definitely defined as above, it does not differ in any sense from the low spinal anesthesia with short-acting agents, such as Novocain. It is the duration of the anesthesia by the particular agent commonly used in saddle block that distinguishes this technique from other techniques. It perhaps justifies our acceptance of a greater incidence of postspinal headache that the Nupercaine ordinarily carries with it as compared to other anesthetics.

DR. CHESTER D. BRADLEY, Newport News, Va.—The impressive work on spinal anesthesia which has been done by Dr. Schmitz and others represents a most wholesome attempt to get away from general anesthesia in obstetrics with its attendant dangers. The hazard of a full stomach is always present and it is doubtful if we are justified in subjecting the parturient woman to the risk of aspiration for the sake of pain relief. So often labor starts after a heavy meal or occasionally a patient will take a snack just before going to the hospital at the urging of solicitous relatives. Even though labor starts as much as three hours after eating, food may remain in the stomach. In a recent case of my own a primipara went into labor three hours after supper. She came into the hospital very soon and had nothing but liquids in the course of labor. During general anesthesia she vomited undigested food which she had eaten twenty-six hours before. On the service of another doctor, the wife of a prominent dentist died on the delivery table under general anesthesia. At autopsy a piece of meat was found obstructing the trachea.

Spinal anesthesia gives a wonderful feeling of safety from this type of complication. Furthermore, one escapes the fetal depression which so often occurs with general anesthesia following heavy sedation of the mother during labor. I confess to a fondness for hearing the newborn baby cry promptly. However, some of us are going to run up against certain difficulties if we attempt to use any form of spinal anesthesia more or less routinely in obstetrics. In the Newport News area where I practice, the public has a deeply rooted phobia against spinal anesthesia. Almost every time I use it I am forced to justify it to the patient and her family. This is not an insuperable obstacle. It could be eradicated by education. However, the headache which occurs so often after spinal anesthesia is a more serious obstacle. I do not let this unpleasant aftereffect deter me from using low spinal anesthesia in selected cases. I use it frequently and I will continue to do so for there are certain types of complicated obstetrical cases in which I feel it is best for both the mother and baby. But I submit that the routine use of any form of spinal anesthesia in private practice is going to give the doctor a lot to explain and justify the postspinal headache to the patient and her family. For this reason I have lately been resorting more and more to pudental block anesthesia for uncomplicated cases.

DR. CHARLES O. McCORMICK, Indianapolis, Ind.—I would like to recommend to this group a form of childbirth pain relief that is free from headache, fall in blood pressure, foot drop and such other handicaps as we have just heard. One that does not involve meticulous technique nor require an expert administrator. In our clinic at Indiana University the administration is performed by the student nurse. The method is simple, extremely safe for both the mother and infant, inexpensive, applicable to practically every woman in labor, and has an efficiency of over 95 per cent. I refer to modified rectal ether analgesia.

DR. CLIFFORD B. LULL, Philadelphia, Pa.—I believe that Dr. Schmitz has brought out two very important findings; one, that the spinal anesthesia must be given by an experienced individual, and second, that the technique must be meticulously carried out. At the present time we are using saddle block in a large proportion of our vaginal deliveries.



I should like to call attention to one or two factors. One, that if the patient is to be delivered within a very short time after the spinal is given it is probably just as well to use a drug which does not last too long. We like to use in cases that are going to be delivered almost immediately, 35 mg. of Metycaine. If the delivery is not imminent and probably will not take place for one or two hours, then we prefer Nupercaine. We have done this because on one occasion we gave a patient Nupercaine and delivered her in about fifteen minutes. Everything went satisfactorily but when the patient went back to her room an hour later, by being moved and changing her posture the anesthesia level rose to the point where she became quite definitely ill. We, therefore, now have the level checked before she leaves the delivery room as we do routinely the blood pressure, pulse rate, and height of the fundus of the uterus. This allows the nurse on the floor to know just where the level was at the time of removal from the operating room and this is tested by her, particularly if she has had Nupercaine used as a drug in the anesthetic. The figures which I quoted in my own paper concerning post-spinal headaches I do not believe to be entirely correct. This is probably due to the fact that the resident neglected to put it on the chart. I can honestly say, however, that we did not become spinal-headache conscious until after we had been using spinal anesthesia in our work for some time. We have not had any that were severe enough to become alarming, and almost all of them were relieved by placing a wasp-girdle on the patient. Sometimes we insert a rubber bladder underneath a scultetus binder and inflate it with air. These patients get almost immediate relief. The results from the use of either spinal or caudal have been so satisfactory in our own clinic that we very seldom resort to general anesthesia. For example, last month, in a total of 132 private patients delivered, there were only 27 of them delivered by the use of general anesthesia.

DR. SCHMITZ (Closing)—Relative to a definition of "saddle block," I think this form of anesthesia received its name from the urologists when they attempted to develop an anesthetic for that section of the perineum which would be placed in the saddle. The entire plan for its use in obstetrics is to prolong the anesthetic effect by making it a hyperbaric solution. One of the important precautions in administering the anesthetic is not having the patient in a sitting position for too long a period, because then the effect is limited to the perineum. Relative to the immediate care of the patient following the delivery, we have instituted what so many obstetricians have described as the care of the patient during the fourth stage of labor. She spends that time in the birth room, with the blood pressure apparatus attached to her arm and the intern does not leave her for an hour or longer until we are assured that there are going to be no complications. Many are using a so-called "recovery room" where the patient is under the constant care of nursing and attending staff. We do not have those facilities, so we carry it on in the delivery room.

## A TEN-YEAR STUDY OF CESAREAN SECTION IN ROCHESTER AND MONROE COUNTY, 1937 TO 1946\*

JAMES K. QUIGLEY, M.D., F.A.C.S., ROCHESTER, N. Y.

WHETHER statistical studies such as this are worth the effort put into them has often been questioned. However, we learn by experience, and reliance upon impressions alone is anything but accurate.

In its study of maternal deaths begun in 1933, the Committee on Maternal Welfare of the Medical Society of the County of Monroe encountered those deaths following cesarean section, and, while many detailed surveys of this operation performed in clinics large and small throughout the country had been made, since few had been published of results in an entire community such as a city, state, or county, it seemed proper that this Committee should attempt to determine just what the experience with cesarean section had been in its own community, the reasons given for its performance, and what was the risk.

Accordingly, under the auspices of this Committee, all cesarean sections done in Rochester and Monroe County during the ten-year period, 1926 to 1935, were studied and published.<sup>1</sup> There were 937 operations in this study and the conclusions drawn were: first, that examination of the hospital records showed that there had been a tremendous increase in the number of indications for the operation and that these indications were not always clearly defined, that in some instances pelvic delivery could probably have been accomplished at no greater risk to the patient; second, that the frequency with which abdominal delivery was resorted to in Rochester was no greater than the average reported by similar studies in the United States, and lower than most; third, that the mortality rate of 2.9 per cent was considerably lower than had been previously estimated, and much below that reported in city-wide surveys made up to this time (1937); fourth, that the low cervical cesarean section showed a much lower mortality rate than the classical operation, and for this reason should be more generally adopted.

Now, at the end of another decade, this survey has been repeated under the same auspices and it is the conclusions of this study of 1,693 cases compared with the first and with others done recently elsewhere that will be presented today.

Eight hospitals are included; however, the two University hospitals, Municipal and Strong Memorial, are grouped as a unit. In addition, there are six other hospitals and they all appear in order as follows: Highland, Park Avenue, Strong Memorial and Municipal (as a unit), Genesee, General, St. Mary's, and Monroe County Infirmary. They will be designated as Hospitals A, B, C, D, E, F, and G. There has been no attempt to separate the ward or staff cases from the private patients; divided statistics would be confusing and would serve no good purpose.

\*Presented at the Fifty-Ninth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 9 to 11, 1948.

TABLE I. INCIDENCE

HOSPITAL	TOTAL BIRTHS	CESAREANS	INCIDENCE
A.	11,525	293	1 in 39 or 2.5%
B.	4,672	160	1 in 29 or 3.4%
C.	13,445	260	1 in 51 or 1.9%
D.	9,393	174	1 in 54 or 1.8%
E.	16,543	525	1 in 31 or 3.1%
F.	12,122	268	1 in 45 or 2.2%
G.	835	13	1 in 64 or 1.5%
Total	68,535	1,693	1 in 40 or 2.4%
1926-1935	37,575	937	1 in 40 or 2.4%

The frequency with which resort was made to abdominal delivery varied in the seven hospitals from 3.4 per cent to 1.8 per cent, almost the same as in the previous survey; Hospitals A and B increased slightly while in D and E there was a decrease, and C remained as before. The rate of 1 in 40 or 2.4 per cent was the same as ten years ago.

There has been no increase in the performance of cesarean section in Rochester in ten years and this rate is lower than in those communities and those hospitals shown in the following table:

City of Philadelphia	1931	2.4%	
	1941	2.8%	
City of Syracuse	1947	3.8%	
State of Massachusetts		3.3%	
Cleveland Maternity	1931-1941	6.1%	
Philadelphia Lying-In	1932-1942	5.8%	{ Private 9.2 Ward 3.6
New Haven Hospital	1935-1944	5.8%	{ Private 9.6 Ward 3.2
Chicago Lying-in	1938-1942	4.43%	
Boston Lying-in	1934-1943	4.2%	
Methodist, Brooklyn		3.9%	
Garfield Memorial, Wash., D. C.	1947	3.7%	
Good Samaritan, Los Angeles	1925-1944	11.0%	
(Annual range of 6.2 to 15.5%)			

Indications

Reasons given for this operation were many, in fact 60 were tabulated and are given in Table II. This is an increase of 100 per cent over 1926-1936.

For convenience this list was shortened by grouping and by inclusion of only the most frequent causes. (Table IIA.) The most striking change since the first survey was the increase in the classification, "Cephalopelvic Disproportion," from 3 per cent to 12 per cent. In general, the indications were better defined and substantiated. Contracted pelvis, often simply given as such or divided into various categories, accounted for 24 per cent of the total; cephalopelvic disproportion for 12 per cent; the hemorrhagic states, abruptio and placenta previa, 14 per cent. In 267, or 15 per cent, previous section was given as the indication; this did not include those cases where the reason for the first section, contracted pelvis or other obstructive cause, was present at the time of the subsequent section. The group, elderly primiparas, was subdivided equally between those operated upon before the onset of labor and those in labor, many after a good trial.

Two patients were operated upon because of hydrocephalus and one was done at the time of appendectomy for suppurative appendicitis and peritonitis. Both are questionable reasons. The rate for eclampsia as an

TABLE II. INDICATIONS

	HOSPITAL							TOTAL
	A	B	C	D	E	F	G	
Contracted pelvis	37	31	41	24	23	29	3	188
Justo-minor pelvis	1	9	7	6	43	4		70
Flat pelvis	22		2	6	28	11		69
Funnel pelvis	4	5	6	13	34	9		71
Rachitic pelvis			1					1
Kyphotic pelvis						1		1
Kyphosis and scoliosis					1			1
Spondylolisthetic pelvis					2			2
"Tilted pelvis"					2			2
Fractured pelvis					3			3
Osteoma of pelvis			1					1
Disproportion (fetal-pelvic)	79	19	1	5	54	48		206
Ankylosis of hips					2			2
Deformed vagina					2			2
Uterine myoma	2		12	5	9	9		37
Ovarian cyst			3	1	2	2		8
Atresia of cervix			4					4
Stenosis of cervix after amputation		4						4
Previous cesarean	38	8	36	34	91	58	2	267
Abruptio placentae	14	6	22	10	29	17	1	99
Placenta previa	17	19	9	21	58	22	2	148
Toxemia	14	7	11	6	42	17		97
Eclampsia	2	1		1	3			7
Heart disease	5	2	14	1	6			28
Pulmonary tuberculosis	1	1	16	6	7	1		32
Diabetes	1		2	1	2			6
Nephritis			5	2				7
Previous pelvic repair	7	1	7	7	7	5	1	35
Previous hard labor			2		1	1		4
Previous hard labor with stillbirths	1	1	7	1	9			19
Previous perforation of uterus			1					1
Elderly primipara, no labor		1	6	2	9	6		24
Elderly primipara after trial labor	5		7	1	12			25
Ruptured uterus	2			1	3			6
Rectovaginal fistula	1	1						2
"Soft part dystocia"		5		1	3			9
Cervical dystocia	7		19	3	2	16		47
Cancer of cervix			1			1		2
Uterine inertia		1		3		4		8
Contraction ring dystocia		1	1		2			4
Trial labor	17	7		8	16	1	1	50
Failed forceps					2	1		3
Transverse position		2	3	4	3	1		13
Other malpresentation	3	1	1	1	3	1		10
Poliomyelitis			2		2			4
Pyelonephritis					1			1
Hydronephrosis					1			1
Cerebral hemorrhage					1			1
Subarachnoid hemorrhage					1			1
Brain tumor			1					1
Purpura			1					1
Chronic atelectasis					1			1
Vasa brevia			1					1
Rh disturbance			1		4			5
Fetal distress	4	1	2			2		9
Prolapsed cord	1					1		2
Ruptured appendix						1		1
Not specified	8	24	3					35
Epilepsy							1	1
Hydrocephalus		1					1	2
Bicornate uterus							1	1

indication was less than ten years ago, 7 operations, with a mortality of 28.6 per cent; this alone is enough to condemn it. In addition to these cases of eclampsia, the only mortality in 525 sections in Hospital E was from eclampsia in an elderly primipara operated upon for toxemia who developed eclampsia postoperatively.

TABLE IIA.—INDICATIONS

	A	B	C	D	E	F	G	TOTAL	RATE (PER CENT)
Contracted pelvis, all forms	64	45	59	49	136	54	3	410	24
Cephalopelvic disproportion	79	19	1	5	54	48	0	206	12
Previous cesarean section	38	8	36	34	91	58	2	267	15
Placenta previa	17	19	9	21	58	22	2	148	8.7
Abruptio placentae	14	6	22	10	29	17	1	99	5.2
Toxemia of pregnancy	14	7	11	6	42	17	0	97	5.1
Heart disease	5	2	14	1	6	0	0	28	1.7
Pulmonary tuberculosis	1	1	16	6	7	1	0	32	1.8
Malpresentation	3	3	4	5	6	2	0	23	1.3
Cervical dystocia	7	0	19	3	2	16	0	47	2.7
Trial labor	17	7	0	8	16	1	1	50	2.9
Elderly primiparae	5	0	13	3	21	6	0	48	2.8
All others	21	19	53	23	57	26	4	203	12.0
Not specified	8	24	3	0	0	0	0	35	1.9

Type of Operation

In the survey ten years ago there were no extraperitoneal operations and the classical section was done almost four times as frequently as the low cervical. In the second ten-year period the extraperitoneal section was done thirty times and the number of classical and low cervical sections were practically equal. In Hospital E the increase in the low flap operation was more striking:

1926-1936	41 per cent low flap operations
1937-1941	60 per cent low flap operations
1942-1946	88 per cent low flap operations

This increase in the frequency of the low cervical operation is not merely limited to Rochester. The New Haven Hospital, Chicago Lying-in, the Margaret Hague, and the Women's of New York all report many more low flap operations than classical. At Boston City Hospital, 91 per cent of the 961 sections done between 1936 and 1946 were of the low cervical type.

TABLE III. TYPE OF OPERATION

HOSPITAL	CLASSICAL		LOW CERVICAL		CESAREAN HYSTERECTOMY		EXTRA- PERITONEAL		NOT SPECIFIED	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
A	132	45	140	47	4	1.3	17	5.7	0	
B	103	64	31	19	0		0		26	16
C	171	65	65	25	24	9.2	0			
D	141	81	23	13	8	4.6	2	1.1		
E	106	20	406	77	6	1.1	7	1.2		
F	133	49	115	42	16	6.0	4	1.5		
G	7	54	6	46	0		0			
	793	46.8	786	46.3	58	3.4	30	1.7	26	1.6

Morbidity

The index used was that of the American Committee on Maternal Welfare, viz., a temperature of 100.2° F. on two successive days not including the

day of operation. This criterion is probably the best single indication of operative complication. However, it does include causes unrelated to the operation such as urinary infection, mastitis, respiratory infections, and, conversely, complications of serious import to the patient may not be manifested by a rise in temperature and may still be considered morbid or even fatal. Illustrations are hemorrhage, atelectasis, dehiscence of the abdominal wound, and the toxic states.

TABLE IV. MORBIDITY

HOSPITAL	CESAREAN SECTIONS	NO. MORBID	RATE (PER CENT)	RATE 1926 TO 1935 (PER CENT)
A	293	107	36	35
B	86*	37	43	50
C	260	100	38	38
D	174	60	34	54
E	525	229	43	34
F	268	66	24	35
G	13	8	61	44
	1,619	607	37	38

Data on morbidity available only for 1942-1946. Adhering to the above index, however, the morbidity for all hospitals was 37 per cent with a range of 24 to 61 per cent.

*Experience Elsewhere.—*

Boston Lying-in	21.1 per cent
Chicago Lying-in	43.8 per cent
Cleveland Maternity	45 per cent
Methodist Episcopal, Brooklyn	53.1 per cent
City Survey, New Orleans	61.3 per cent

*Conditions Influencing the Morbidity Rate.—*

Length of labor, rupture of the membranes, and vaginal examinations are three factors considered by most obstetricians in deciding for or against operation.

TABLE V. FACTORS INFLUENCING MORBIDITY

HOSPITAL	PATIENTS IN LABOR		EXAMINED VAGINALLY		MEMBRANES RUPTURED	
A	116		14		44	
B	43		12		12	
C	48		42		37	
D	33		19		25	
E	220		67		85	
F	99		57		59	
G	1		3		0	
Total	560	33%	214	12%	262	18%
	276 morbid or 47%		124 morbid or 58%		141 morbid or 53%	

Many of the 560 patients in labor underwent long tests, real trial labors; 245 had labors of over 24 hours for an average of 39 hours, 36 minutes each. Most women examined vaginally were examined only once, a few twice, and two three times. Two hundred sixty-two cases, or 18 per cent, had ruptured membranes before operation. Time elapsing after rupture of the membranes was over twenty-four hours in many cases and in one five days. There was a rather close correlation of these three factors to the morbidity as expressed in febrile reaction, though some patients sectioned after long labors had no postoperative fever, and, conversely, many were febrile following elective operations where the membranes were intact and there was no vaginal exploration.

*Relation of Patients in Labor to Morbidity.—*

Of 560 in labor, 276 were morbid, 47 per cent as against a general morbidity rate of 37 per cent. Two hundred fourteen women were examined vaginally and 124, or 58 per cent, were morbid. In 262 the membranes had ruptured before operation and 141 were morbid, a rate of 53 per cent against 37 per cent.

**Sterilization**

In 254 operations the patients were sterilized, 15 per cent of the total. Most of these were done by the Madlener technique. In Hospital F the sterilizations were limited to those cases requiring hysterectomy.

**Additional Surgical Procedures at the Time of Cesarean Section**

One appendectomy was done for suppurative appendicitis. Myomectomy for fibroids was performed on fifteen patients, and one patient was sectioned at term because of myomectomy in her third month. There was one case of placenta accreta for which hysterectomy was done.

**Repeat Operations**

There were 442 repeat sections. The indication given in 267 cases was simply previous cesarean section. This leaves a balance of 175 where the reason for the first section was still present such as contracted pelvis or healed pulmonary tuberculosis or previous pelvic repair. Of course some of the patients in this study were subsequently delivered through the pelvis, just how many was not determined.

TABLE VI. NUMBER OPERATED UPON BY OBSTETRICIANS

HOSPITAL	TOTAL CESAREANS	OPERATED UPON BY OBSTET.	NUMBER OF OBSTET.	OPERATED UPON BY SURGEONS	NUMBER OF SURGEONS	OPERATED UPON BY GENERAL PRACTITIONER	NUMBER OF GENERAL PRACTITIONERS
A	293	286 97%	15	7	5	0	0
B	140	115 82%	10	25	5	0	0
C	260	260 100%	18	0	0	0	0
D	174	161 91%	12	13	5	0	0
E	525	517 98%	15	3	2	5	2
F	268	237 88%	5	31	9	0	0
G	13	12 92%	5	1	1	0	0
	1,673	1,589 95%	80*	80 4.7%	27	5	2

\*Thirty-four different obstetricians operated.

Of 1,673 cesarean sections, 1,589, or 95 per cent, were done by obstetrical specialists of whom there were thirty-four, all occupying positions on obstetrical staffs and practically all of them limiting their practice to obstetrics. Fifteen are diplomates of the American Board of Obstetrics and Gynecology. There were five patients operated upon in the early years of this series by two general practitioners assisted by staff obstetricians. Eighty operations, or nearly 5 per cent of the total, were done by twenty-seven general surgeons.

**Fetal Mortality**

Obstetrical and other causes for fetal mortality were: abruptio placentae 41, placenta previa 23, eclampsia and toxemia 12, asphyxia and atelectasis 8, erythroblastosis 3, congenital heart disease 3, other congenital abnormalities 4, pneumonia in infant 1, cerebral hemorrhage 1, unknown 35.

TABLE VII. STILLBIRTHS AND NEONATAL DEATHS

Hospital	A	22
	B	12
	C	28
	D	10
	E	40
	F	20
	G	2
		134 or 7.9 per cent uncorrected*

\*Including many premature and some nonviable infants.

A fetal mortality rate of 7.9 per cent seems high for an operation frequently done in the interest of the child. Forty-one deaths resulted in the cases of abruptio placentae, which carries a high infant mortality rate under any treatment. These were almost all stillbirths. Placenta previa accounted for 23 and eclampsia and toxemia for 12. These three causes took 76 fetal lives, about 60 per cent of the 134 lost. Asphyxia and atelectasis were responsible for eight, a not unusual proportion. There were only six congenital abnormalities such as spina bifida, congenital heart disease, etc. Earlier diagnosis and treatment of premature separation and placenta previa would help to lower the infant death rate in cesarean section. Only assistants properly trained in resuscitation of the newborn should be entrusted with this detail in the operating room.

Maternal Mortality

The portion of this survey dealing with maternal mortality is the most interesting and encouraging feature of the study, for all hospitals showed an improvement and the rate for the entire city was only one-third that of ten years ago. Sixteen deaths in 1,693 operations gives a rate of 0.94 per cent which is very low for this type of survey, though a few individual hospitals have reported several hundred cesarean sections with a rate of less than 1 per cent. In this series the rate per hospital varied from 7.69 per cent, where 1 death occurred in 13 operations, to 0.19 per cent in another hospital, where one patient died in 525 cesareans.

TABLE VIII. MATERNAL MORTALITY

HOSPITAL	CESAREANS	DEATHS	RATE (PER CENT)	RATE 1926-1935 SURVEY (PER CENT)
A	293	2	0.68	2.1
B	160	5	3.12	7.4
C	260	2	0.76	2.5
D	174	2	1.14	5.1
E	525	1	0.19	1.1
F	268	3	1.12	4.2
G	13	1	7.69	11.0
Total	1,693	16	0.94	2.9

Ten to fifteen years ago there was an impression that the death rate for abdominal delivery the country over was at least 5 per cent, though many clinics at this time had reported lower rates.

Table IX shows the improvement in other communities and the present low rates in some of the largest lying-in hospitals.



TABLE IX. AN IMPROVED CESAREAN SECTION MORTALITY RATE

HOSPITAL	YEAR	NO. SECTIONS	PER CENT
Philadelphia entire city	1931		6.1
	1935		4.6
	1940		1.8
State of Mass.		11,030	2.4
Philadelphia Lying-In	1932-1937	665	2.55
	1937-1942	657	1.37
Boston Lying-in	1934-1938	912	1.9
	1939-1943	975	0.7
Chicago Lying-in	1931-1944	1,790	0.61
	1942-1944	317	0.00
Methodist, Brooklyn	1920-1938	1,066	3.18
Johns Hopkins	1922-1931	386	4.4
	1932-1941	750	1.7
Cleveland Maternity	1931-1941	1,317	1.7
Rochester General	1938-1948	604	0.00
Five United States Maternities since 1931 (Collected by Dieckmann)		6,335	1.46

TABLE X. MORTALITY OF TYPES OF CESAREAN SECTION, ROCHESTER

	OPERATIONS	DEATHS	RATE (PER CENT)	RATE 1926-1935 (PER CENT)
Classical	793	11	1.38	3.34
Low cervical	786	2	0.25	1.02
Cesarean hysterectomy	58	1	1.72	8.69
Peritoneal exclusion	30	2	6.66	
Not reported	26			

The rate for the low cervical operation in the first ten-year study in Rochester was one-third that of the classical operation, and in the second series less than one-fifth, in spite of the fact that in many institutions the low flap cesarean is performed almost entirely upon patients after trial labors and the classical operation is reserved for the elective cases. Further proof of desirability of the low cervical operation because of its lower risk is shown in the following table collected by Dieckmann:

TABLE XI. MORTALITY OF TYPES OF CESAREAN SECTION

HOSPITAL	CLASSICAL		LOW CERVICAL	
	NO.	MORTALITY (PER CENT)	NO.	MORTALITY (PER CENT)
Margaret Hague	117	6.8	1,261	1.03
Boston Lying-in	372	2.1	168	4.20
Chicago Lying-in	22	18.1	1,618	0.38
Women's Hospital, N. Y.	235	4.3	620	2.10
Total	746	4.0	3,667	1.07
Collected by F. Irving	3,334	6.7	2,006	1.85

For at least twenty years the writer has urged the more general adoption of the low flap technique in all cesarean sections<sup>2</sup> and the observation made in the first ten-year report in Rochester is here repeated: "One cannot escape the conviction that the mortality rate for the low cervical cesarean section or laparotrachelotomy is one-half or even less than one-half that of the classic operation—it must therefore be safer and should be more generally adopted. In addition to many other advantages there is notably less liability for rupture of the uterus in subsequent pregnancies."

TABLE XII. FATALITIES

HOS- PITAL	YEAR	INDICATION	TYPE	LABOR (HOURS)	VAGINAL EXAMINA- TION	MEM- BRANES RUPTURED	AUTOPSY	CAUSE OF DEATH	AGE	PARA	DAYS POST- PARTUM
A	1941	Desire of patient	Hurst	0	1	24	0	Sepsis	32	ii	14
	1940	Eclampsia	Classical	0	0	0	0	Eclampsia	22	0	2
	1938	Face presentation fibroids	Classical	0	0	0	0	Peritonitis	42	0	16
C	1939	Disproportion	Classical	30	0	0	0	Pul. embolus	28	0	16
	1940	Transverse position	Classical	30	2	Artificial	Yes	Peritonitis	37	0	42
	1942	Contracted pelvis	Classical	37	2	0	0	Pul. embolus	26	ii	4
	1942	Disproportion	Classical	48	0	0	0	Peritonitis	21	0	19
	1941	Previous repair	Low cervical	48	1	0	0	P.P. hemorrhage	35	iii	1
D	1944	Rh, heart disease	Classical	0	0	3	Yes	Rh. ht. dis.	25	0	27
	1941	Eclampsia	Low cervical	0	0	0	Yes	Thrombosis carotid artery	36	0	10
	1943	Placenta previa	Classical	0	1	0	Yes	Peritonitis	42	0	7
E	1938	Toxemia	Classical	0	0	0	0	Eclampsia	38	0	8 hr.
F	1937	Disproportion	Classical	0	0	0	0	P.P. hemorrhage	31	0	6 hr.
	1941	Justo minor	Classical	0	0	0	Yes	Peritonitis	32	0	4
	1946	Abruptio	Cesarean hysterec- tomy	0	0	0	0	Peritonitis and heart disease	32	ii	6
	1942	Disproportion	Attempted Waters' operation	36	2	15	Yes	Peritonitis	20	0	13

TABLE XIII. MORTALITY OF VARIOUS CONDITIONS TREATED BY CESAREAN SECTION

	NUMBER	DEATHS	RATE (PER CENT)
Abruptio placentae	99	1	1.00
Placenta previa	148	1	0.67
Eclampsia	7	2	28.60
Heart disease	28	1	3.50
Toxemia	97	1	1.00
Pulmonary tuberculosis	32	0	0.00
Contracted pelvis and disproportion	616	5	0.81

*Causes of Death.*—

Peritonitis	7
Sepsis	1
Postpartum hemorrhage	2
Eclampsia	2
Pulmonary embolism	2
Rheumatic heart disease	1
Thrombosis carotid artery in an eclamptic	1

While it is often claimed that cesarean section is blamed for deaths due to the condition requiring operation, 11, or 68 per cent, of the deaths in this series were attributable to the operation.

One hundred forty-eight cases of placenta previa with one death and a single fatality in 99 cases of abruptio placentae is a low rate indeed, while 28.6 per cent mortality for eclampsia treated by cesarean section simply confirms the impression that these patients are not good risks for this method of delivery.

**Conclusions**

Two surveys of ten years each on all cesarean sections performed in all the hospitals, large and small, in a community of 400,000 showed a low incidence of this operation in both surveys. The mortality rate was low; for the second period only one-third that of ten years ago, viz., 0.94 per cent, and this is the lowest rate ever reported for a community survey.

Forty-six per cent of all operations were of the low flap variety and the mortality of this type of operation was less than one-fifth that of the classical operation. There were no deaths from peritonitis or sepsis in this group; the two deaths following the low flap operation were due one to hemorrhage and the other to thrombosis of the carotid artery in an eclamptic.

Factors which probably contributed to a mortality rate one-third that of the first survey ten years ago were: First, 95 per cent of the operations were done by obstetrical specialists. Consultation is compulsory in all complicated obstetrical cases in all hospitals. Second, chemotherapy and penicillin were employed. Third, the value of early and sufficient transfusions was recognized. Fourth, all cases received better maternal care. All these were reflected in a low general maternal mortality rate—6 per 10,000 in 1944, or 2.8 per 1,000 births, 1933 to 1944, for the county.

If 1,693 sections in hospitals large and small have a mortality rate of approximately 1 per cent, this rate should not be exceeded by well-staffed maternities. It is more important to consider the contraindications for the operation than the indications.

**References**

1. Quigley, James K.: New York State J. Med. 40: 699, 1940.
2. Quigley, James K.: New York State J. Med. 25: 49, 1925.

**Discussion**

DR. LOUIS E. PHANEUF, Boston, Mass.—Dr. Quigley's second survey of cesarean sections for a ten-year period in Rochester and Monroe County is a valuable contribution to the subject. This second survey shows the adoption of the extraperitoneal cesarean section,

and a high increase in the number of low or cervical cesarean sections with improved results. The improvement in maternal mortality is to be commended as this is very low. We must bear in mind that the mortality of cesarean section is governed, to a certain extent, by the type of patient on whom the operation is done. It is always higher in the neglected case than it is in the clean case, in which there have been no labor nor examinations.

Ninety-nine cases of abruptio placentae with but one death, and one hundred forty-eight cases of placenta previa with but one death is indeed an excellent record.

In order to discuss Dr. Quigley's paper, I have looked up my personal cesarean sections from Jan. 1, 1938, to Jan. 1, 1948, and find that during this period of ten years I have done one hundred ninety-six operations, divided as follows: transverse cervical cesarean sections, 162; extraperitoneal cesarean sections, 12; peritoneal exclusion cesarean sections, 4; low classical cesarean sections, 8; and Porro cesarean sections, 10. In this group there were 69 cesarean sections, or 30.1 per cent, which were repeat operations, and 127 cesarean sections in which the indication was other than a repeat operation—12.7 operations per year.

The indications for the classical cesarean sections, which I seldom do, were: Uterus adherent to the abdominal incision from previous sections, so that the uterus was incised without entering the peritoneal cavity, four cases; and lower segment not formed in premature delivery, four cases, or a total of eight classical cesarean sections in the group.

The maternal mortality was 4 in 196 cases, or 2 per cent.

CASE 1, June 20, 1939.—Died of shock and hemorrhage after a Latzko extraperitoneal operation.

CASE 2, Aug. 25, 1939.—Died of embolism on the hospital steps, as she was going home, on the twelfth postoperative day, following a transverse cervical cesarean section.

CASE 3, Jan. 30, 1941.—Died after a transverse cervical cesarean section; the autopsy showed: "General plastic peritonitis, primary in the left tube and ovary. Uterus clean and healing."

CASE 4, June 5, 1941.—Died of hemorrhage from a central placenta previa, following a classical cesarean section.

The fetal mortality was 9 in 196, or 4.5 per cent. Death was ascribed to the following causes: stillborn, 3; purpura hemorrhagica, 1; monster, 1; and prematurity, 4.

DR. FREDERICK H. FALLS, Chicago, Ill.—The discussion of all of the papers on cesarean section at this meeting has been pointed at the difference between the low cervical and classical type of cesarean section stressing the difference in mortality between the two operations. The outcome in fatal cases, in my opinion, is due not to whether a low cervical or a classical operation is done, but to who does the operation, and why it is done, and the condition of the patient, when the indication for the cesarean section arises. There is only one way that one can determine which is the better operation and that is for the same man to alternate these operations in consecutive cases. We have been doing this for a number of years, and have approximately 250 cases. As far as we can see, whether you make the incision in the uterine musculature within an inch of the symphysis pubis, or within 3 inches of the symphysis pubis, it does not make much difference. It sometimes happens that cesarean section is the best way out of a desperate situation. I remember a patient with a severe frontal sinus infection which had been drained. She had been transferred to the contagious hospital at the University of Iowa because erysipelas developed in the frontal wound, and when I first saw her she was in the erysipelas ward and had a temperature of 104° F. and had had four eclamptic convulsions. It was hardly a case that one would want to elect for cesarean section. Under the circumstances I felt that the baby had some chance, the mother almost none. I heard the heart tones and noted that the woman was 32 weeks pregnant. I took her down to the basement (they did not have an operating room) where they did the postmortem examinations, put her on the table, opened the abdomen, took out the live baby and decided I might as

well take out the uterus so she would not die of puerperal sepsis even if she did develop streptococcal peritonitis. The woman did not die and the baby did not die. I took a chance on spoiling my statistics for cesarean section. If I had done either classical or low cervical and if the woman had died the case would have been one against whatever operation I had performed, which would have been manifestly unfair to that operation. It seems to me in all of our statistics of this kind we must determine and take into consideration whether the mortality can be proved to be due to the operation, or whether the mortality is due to the condition for which the operation is undertaken.

DR. NICHOLSON J. EASTMAN, Baltimore, Md.—The statistical analysis of several hundred case histories, even in one's own hospital, is quite an undertaking, and Dr. Quigley has presented a searching statistical analysis of 1,693 cases from seven different hospitals, and simply on the basis of the labor entailed he is to be complimented on the vast amount of information this observation brings forth. I will limit my remarks to one topic; namely, one of the important frequent indications for cesarean section, cephalopelvic disproportion.

In this study, 206, or about one-eighth of the cesarean sections, were done because of cephalopelvic disproportion. In Hospital A, one-fourth of the sections were on the basis of cephalopelvic disproportion; in Dr. Hennessy's series it was the second, and in Dr. Lull's, it was the most frequent indication. Cephalopelvic disproportion is an imposing term, it is widely accepted as a legitimate reason for cesarean section and, of course, is deeply entrenched in our literature. Nevertheless, I should like to raise some questions as to its validity.

If we go back to Dr. Quigley's report, in Hospital A, some 79 cesarean sections were done in the course of several hundred for cephalopelvic disproportion, one-fourth for that reason; in Hospital C in the course of 160 only one was done because of cephalopelvic disproportion. This shows a lack of uniformity in the use of this term in the two hospitals and, by the same token, a difference in the way of thinking about cephalopelvic disproportion. Another observation that is pertinent to the question may be based on Dr. Quigley's list of indications. Whereas there are 206 cases of cephalopelvic disproportion, there are also some 400 cases of contraction of the pelvis.

Now, in general, the term cephalopelvic disproportion carries with it the connotation of contracted pelvis, and the question comes up as to why it is necessary to have this group of cephalopelvic disproportion, plus the group of contracted pelvis. There are several explanations that might make this plausible. You may have cephalopelvic disproportion without contracted pelvis because of an excessive size child. This is seen in less than 1 per cent of cases and does not loom large. Disproportion may be due to an occiput posterior presentation, giving larger diameters of the head to go through the pelvis. This may account for some of these cases without a contracted pelvis. Nevertheless, if this be true I should think it would lead to clarity to regard occiput posterior as the indication. In some cases of cephalopelvic disproportion, the pelvis may be slightly small and the baby slightly large and it is difficult to tell just which of these is the predominating cause of dystocia. We all know that such cases occur not infrequently but I doubt if they occur as often as these figures would indicate.

There is still another explanation which is probably the right one, namely, that the cases designated as cephalopelvic disproportion were instances of uterine inertia. The patient enters the hospital with the fetal head high; the cervix does not dilate, and after sixteen to eighteen hours, things come to a standstill, and it is decided that something must be wrong. Since the head does not come down, the dystocia is assigned to cephalopelvic disproportion. Every year we see twelve or fifteen cases in which a baby has been previously delivered elsewhere by cesarean section because of cephalopelvic disproportion. We have studied these pelvises by x-ray and in most instances the pelvis has been perfectly normal, and in many decidedly large. In quite a number we have delivered these women vaginally of infants much larger than the previous section baby. Hence, I am a little skeptical about this term, believe it is abused and that its use is often due to failure to recognize uterine inertia rather than any actual lack of space.

DR. LEWIS F. MC LEAN, Buffalo, N. Y.—Allow me to review briefly our cesarean section record for the past ten years at the Millard Fillmore Hospital, Buffalo, New York.

Our active staff consists of fourteen members, eight of whom have a diplomate status. The remainder are junior members who limit their practice to obstetrics and gynecology and expect to qualify for their boards. This nucleus supervises the work of about one hundred practitioners who have courtesy privileges in obstetrics.

The accompanying table shows the record of sections for the ten years, 1937 to 1947, inclusive. The section incidence is relatively high, varying from 6.2 per cent to 10.8 per cent. Between the years 1937 to 1947, inclusive, the section mortality rate varied from 4.3 per cent to 1.1 per cent. In the years 1946 and 1947 it dropped to zero.

TABLE I

YEAR	DELIVERIES	SECTIONS.	SECTION MATERNAL.	
			PER CENT SECTIONS	MORTALITY RATE (PER CENT)
1937	1426	154	10.8	1.8
1938	1725	139	8.0	2.5
1939	1441	132	9.16	4.0
1940	1866	119	6.3	4.3
1941	2265	139	6.2	1.4
1942	3067	193	6.3	1.0
1943	3773	302	8.0	2.6
1944	3095	256	8.2	1.1
1945	3123	241	7.6	0.8
1946	3578	308	8.1	0
1947	4049	334	8.2	0

Our last cesarean death occurred in November, 1945. Since that time, in a period of two years and ten months, nearly 900 sections have been performed with no maternal deaths.

This marked reduction has paralleled a similar reduction in the obstetrical maternal mortality. From the years 1940 to 1944, inclusive, the maternal mortality ranged from 0.13 per cent to 0.4 per cent. In 1946, it dropped to 0.058 and in 1947 to 0.049 per cent. This marked drop can be ascribed in part to better blood bank facilities, increased resident staff, antibiotics, etc. We believe, however, that the change was mainly due to the institution of an obstetric recovery room in September, 1945. A review of our maternal deaths disclosed that many of them occurred in the several hours following delivery, and apparently could have been prevented by vigilant supervision and vigorous treatment.

We placed eight beds in two unused rooms in the delivery wing. Every postpartum patient remains there for eight hours following delivery. A graduate nurse is in constant attendance and notes the pulse, blood pressure, amount of flow, condition of the fundus, etc., and records the data on a special chart.

If any abnormal signs (that is, abnormal bleeding) occur, the Resident is called and undertakes remedial measures at once. These may include exploration of the birth canal, suturing, ligation of bleeding vessels, packing, transfusion, etc. A supply of Type IV O, Rh-negative blood with Witbsky anti-A and anti-B substance is available on the delivery floor at all times and can be given immediately. We do not give plasma or saline infusions in hemorrhage cases. Blood is always immediately available and is always given.

We believe that the above measures have made cesarean section a safe procedure in our hospital. Accordingly, we do not hesitate to employ it when we think that the well-being of mother and child demand its use.

## OVOGENESIS IN THE ADULT HUMAN OVARY\*

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IT HAS been taught for many years that the primordial ova are all formed by the time of birth. The number in each ovary has been stated to vary between 100,000 and 400,000. The discrepancy in these numbers is due perhaps, as Simkins has so well pointed out, to the fact that the methods used in making these counts were only approximate ones. Evans and Swezy, some twenty years ago, became interested in ovogenesis in mammals and they showed conclusively that ovogenesis in the rat, guinea pig, dog, cat, and man occurs throughout the whole active period of the estrous cycle. They presented some material from the human being and came to somewhat similar conclusions as regards the menstrual cycle. In the rat, guinea pig, and dog, the follicular cycle coincides normally with the estrous cycle. They felt that in man the follicular cycle had no necessary relation to the menstrual cycle, ovulation taking place at any time during the menstrual cycle. They claimed that the ova arrived from proliferations of the germinal epithelium in the form of invaginating cords forming groups of epithelial cells which cut off from the epithelium and passed through the tunica albuginea. These cell groups pass into the cortex, enlarge, and some develop into sex cells, the remaining epithelial cells in the group forming the living follicular cells.

Extensive degeneration of the sex cells is a normal process in each cycle. It occurs at all periods, but is at its maximum at the anestrus or proestrus in mammals. Degeneration is seen both in cells and in the ovum. In man there is a somewhat similar relationship of ovogenesis to the ovulation cycle which seems to characterize the mammals generally. Evans and Swezy feel that ovulation in man occurs at approximate intervals of 28 days, but this rhythm bears no exact or invariable relationship to the menstrual cycle. The concept that in the mammals the ova are all formed before birth and remain quiescent until cycle maturity has no foundation in fact. On the contrary, all of the ova of adult life are new formations and are being constantly produced and are constantly being destroyed. It was always our impression that ovulation in the human being in a 28-day cycle occurred, usually, between the fourteenth and eighteenth days. We felt this was clearly shown by the work of Allen, Pratt, Newell, and Bland in 1930.

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Simkins, in 1932, studied the maturation of the human ovum. He, as well as Swezy and Evans, has described minute changes in the maturation of the ovum up to birth. After birth, these changes do not occur and are, therefore, of no special interest in this review of a study of the more mature ovary. In adult life, the only change as regards maturation is the extrusion of the first and second polar bodies at the time of ovulation, a rearrangement of the Golgi apparatus, changes in the yolk granules and mitochondria.

Simkins shows an interesting table concerning the number of ova present at birth to 14 years. He divides the undeveloped follicles into two groups, the primordial follicles and the primary follicles. He described a primordial follicle as an ovum which is inconstantly and incompletely surrounded by flat and ellipsoidal cells and the primary follicle as one which is completely and constantly surrounded by rounded cells. The primordial follicles have an average diameter of 30 microns and the primary follicles of 50 microns. At birth he estimates 115 primordial follicles in the low-power field with only three primary. At 14 years of age, the primordial follicles are reduced to the low average of three to a low-power field and the primary follicles remain the same.

TABLE I. (SIMKINS)

AGE	PRIMORDIAL FOLLICLES IN LOW-POWER FIELD	PRIMARY FOLLICLES IN LOW-POWER FIELD	ESTIMATED NUMBER IN ONE OVARY
At birth	115	3	143,000
5 months postpartum	78	4	112,000
6 months postpartum	48	3	86,000
3 years	41	4	79,000
7 years	16	4	48,000
8 years	18	3	23,760
9 years	9	4	18,000
14 years	3	3	10,500

In this table, Simkins shows the marked diminution of follicles from birth to 14 years, inclusive. This diminution is due chiefly to the primordial follicles, the primary follicles being comparatively few from the beginning. For Simkins' definition of primordial and primary follicles see text.

The chief difference in the work of Evans and Swezy and Simkins is that they disagree as to the origin of the new ova in the adult ovary. Simkins feels that there is no activity of the germinal epithelium after birth, that the tunica albuginea is inactive and there are no tubes or cord cells ramifying into the stroma of the ovary carrying with them new gonocytes throughout the period of cycle fertility. He feels that new ova arise from the cells of a neogenic zone which are not to be considered as germ cells, but somatic cells induced to grow into germ cells by the follicular stimulating hormone of the anterior lobe of the hypophysis. This supposition brings our attention to the so-called cortex of the ovary which, heretofore, has not been recognized as a parenchymatous part of the organ and usually is described as entirely connective tissue. We shall elaborate further concerning the appearance and structure of the cortex in reviewing our own observations.

In studying the work of these investigators, this rather controversial idea as to direct origin of the germ cells was most interesting. We think it rather amazing and somewhat disturbing that such a subject, which might suggest definite changes in therapy in treatment of certain clinical conditions—chiefly, sterility, amenorrhea and the anovulatory cycle, has not been discussed among the gynecologists in relationship concerning the facts in these two very important



contributions. No adequate work has been done with the view of presenting further evidence of the presence of the admitted newly developing ova in adult life. It is also remarkable that in the latest editions of textbooks on gynecology and obstetrics, in discussing the histology of the ovary, there has been no noticeable change made concerning the long-accepted older view of nonproduction of new ova after birth. Novak mentions the new subject in passing, but feels that further investigation is necessary for definite conclusions. Hamblen also refers to this work in his monograph. In 1934, in his textbook on histology, Cowdry mentions the contentions of Evans and Swezy in some detail and apparently accepts them as well in man as in other mammals.

For some time we have thought it might be of interest to review some additional human material in the attempt to determine what this situation might mean to us. Accordingly, we selected at random from recent files of our gynecological service, which have accumulated for many years, sections of ovaries from operative material which have been removed from patients in various decades of life, about 800 in number. The more recent files were considered because of better staining and better fixation, the routine being that the specimens are placed in 10 per cent formalin in the operating room. Fixation, therefore, in most cases was adequate and particularly since the very detailed minutiae of the study of maturation of the ovum before birth were not a part of this study, we feel that our material is fairly representative. These sections were studied in connection with their clinical history in which the age and the menstrual history could be obtained in the vast majority of instances. In addition to reviewing the character of the ovary from late fetal life through to adult life by means of some good autopsy material, we wished to study particularly the character of the germinal epithelium, the tunica albuginea, the cortex, the type and number of follicles present, as well as the picture of the corpus luteum.

### Material

The changes in the germinal epithelium and the tunica when active presented themselves very strikingly and without going into great detail concerning these changes, we shall rather point them out in the descriptions in the legends of the accompanying illustrations. Much of the material is from patients over 40 years of age, but after assorting the specimens approximately 300 were available between 20 and 40 years. In studying the corpus luteum and the menstrual history together, we were able fairly accurately to approximate the day of cycle. We shall refer to this point later.

Schroeder in 1928 described the human ovarian cycle. He divides the ovary into various parts, into the germinal epithelium, the tunica albuginea, the cortex, and the medulla. With this description of the adult ovary most authorities agree. He illustrated a very interesting large section of a two-year-old whole ovary which we have copied to compare to one of similar age in our series. Quoting from Evans and Swezy, Schroeder felt that a great impulse is given to many follicles about the time that one or two are maturing. The small or medium follicles are more numerous when the large follicles are present and later when the corpus is formed. With this, our findings do not coincide. He also found that some, especially larger ones, become atretic, the greatest number of atretic follicles being found at the time of the formation of the corpus. These findings he considered rhythmical. Swezy and Evans feel that in some of their

cases the follicular cycle coincided with the menstrual cycle; that is, the number of ova present during the first few days was very small, and in others during the middle of the cycle the number was slightly larger and the maximum was reached during the last few days of the cycle. In the greater number of cases, however, they felt that there was no recognizable relationship between the condition of the ovary and the period of the menstrual cycle.

To review this point we selected specimens from individuals between 20 and 40 years of age. In the first place, during these decades the number of ova and the ovarian function are still adequate, but, because of the lesser number of ova than in the previous decades, we felt that differentiation as to what is actually going on could be better determined. Fifty selected cases were studied. The presence of small follicles, the condition of the tunica and germinal epithelium, the activity of developing follicles, and the character of the corpus luteum were studied in regard to variations in different parts of the menstrual cycle. A very detailed chart concerning these observations was prepared, but owing to the fact that it was quite cumbersome for publication, we decided to submit the results of this rather detailed study in the form of a summary.

In general, there was a very striking tendency for follicular activity to correspond to the menstrual cycle, more so in our series than Evans and Swezy indicated. The activity of the germinal epithelium and the tunica albuginea was definitely more pronounced in the early part of the cycle. The number of small follicles was more conspicuous in the earlier part of the cycle up to the time of usual ovulation. The developing follicles were most conspicuous just before the time of usual ovulation and continued more prominently till about the twenty-second day of the cycle. The histological characteristic of the corpus luteum fitted in very well with its time in the menstrual cycle. The number of small follicles did not go hand in hand with most mature follicle development as Schroeder contended.

The cortex was most interesting to us. It is described usually as connective tissue. For a long time one of us has contended that the cortex is not actually a connective tissue because it does not show the staining properties with van Gieson stain for such tissue, nor with Masson stain. In the van Gieson stain the cortex stains chiefly a yellow color as does ordinary smooth muscle tissue. A deeper red connective tissue stain is shown in the superficial portion of the ovary, namely, in the tunica. In many instances, the cortex and the tunica appear as one active cellular structure. In others, the tunica appears as a less cellular structure and frequently the tunica albuginea and the cortex are two clearly distinct zones. Almost invariably, with primordial or developing ova in the cortex, the staining reaction of the surrounding particle cells is much deeper and they appear definitely larger with this association than at other times. Intensity in nuclear staining is quite variable and we feel that the deep staining is most striking when functional activity is greatest. We regard the cortex not as smooth muscle nor as fibrous tissue, but as a hybrid tissue having some definite function as yet unknown.

Again, the details of our findings will be shown in our illustrations and are fully described in the legends. In reviewing our findings, we wish to state the following: In the first place, the germinal epithelium throughout the functional period of the ovary shows marked activity in growth, sending groups of cells which subsequently break off into the underlying tissue and finally reach the deeper cortex. New ova can actually be seen in association with this new development. The cells arrange themselves in perpendicular groups in the tunica immediately beneath the germinal epithelium, and subsequently invade. In the overlying tissue this activity does not involve the entire surface of the ovary, but rather occurs in spots. Whether these wandering cells, as we have termed them, develop into ova at once, or disintegrate immediately or subse-

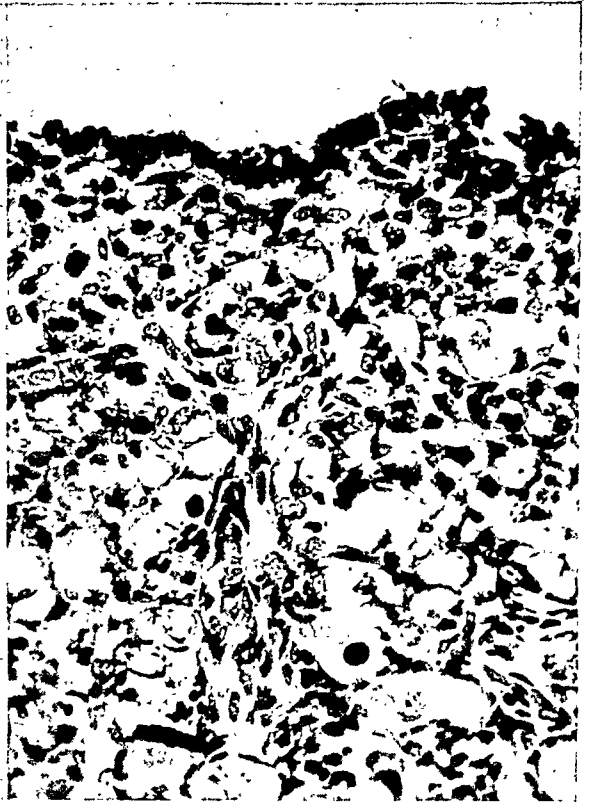
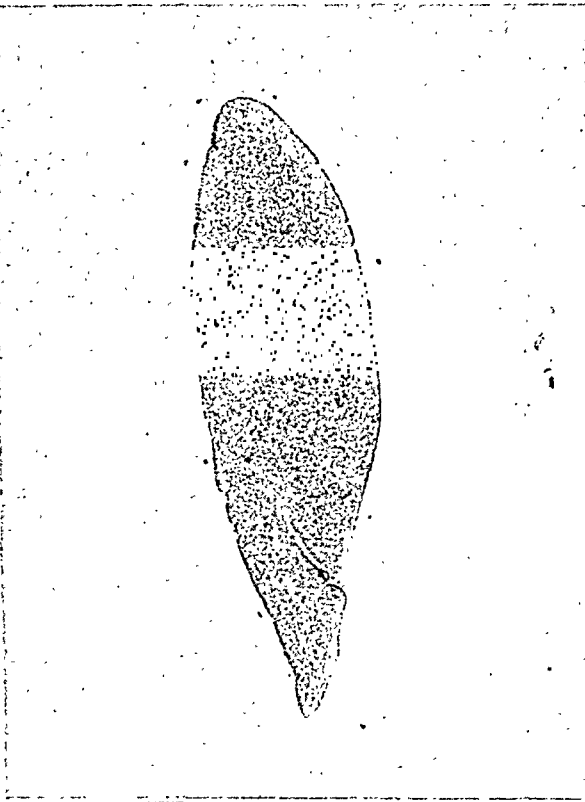


Fig.

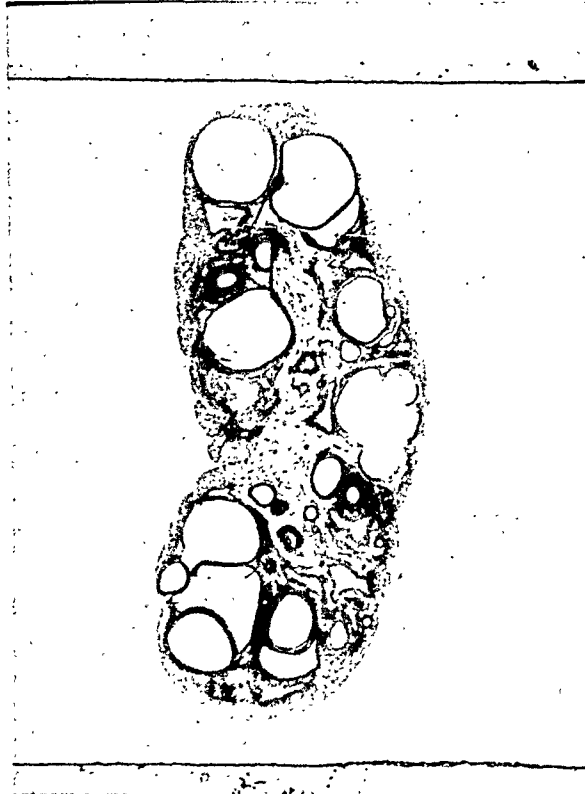


Fig.

Fig. 1.—Ovary, six months' gestation fetus, section of whole ovary, active germinal epithelium can be seen in different areas. Main substance made up chiefly of primordial follicles (Stinkins) with a small medulla being invaded by them. Cortex practically one mass of follicles.

Fig. 2.—Ovary, six months' fetus, low power showing active germinal epithelium on surface with underlying substance practically made up of primordial follicles, and some primary follicles.

Fig. 3.—Ovary, two years old, whole section, surface lined with thickened germinal epithelium, many small follicles in tunica and cortex, several large cysts undergoing cystic atresia. Cortex showing well; medulla comparatively small.

Fig. 4.—Ovary, two years old, high power, showing markedly active germinal epithelium with underlying tunica and cortex crowded with many primordial and primary follicles, structure of ova well seen. Note primary follicle just to right showing two ova encased in one follicle.

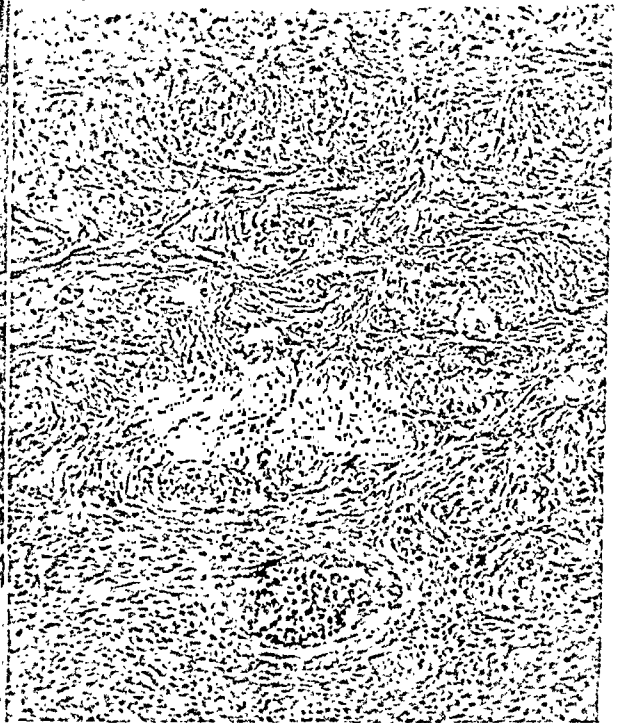
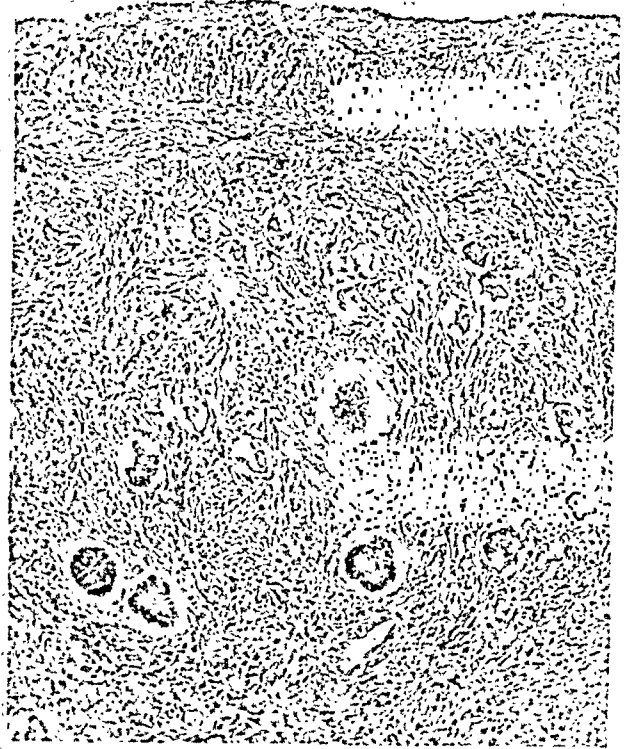


Fig. 5.—Ovary 12 years old, gross section whole ovary. Cortex and tunica well shown, medulla coming in from right center. Several maturing follicles dispersed evenly throughout the cortical portion of the section. Note the lower maturing follicle invading medulla.

Fig. 6.—Ovary, 12 years old, low power. Germinal epithelium flat, tunica active, numerous primary follicles in superficial cortex, with cell nests and more advanced follicles showing in deeper cortex.

Fig. 7.—Ovary, 19 years old, gross picture, showing larger portion of ovary. Medulla coming in right central portion. Numerous scattered cystic follicles, some invaded into medulla. No fresh corpus luteum seen, but one present from previous ovulation.

Fig. 8.—Ovary, 19 years old, low power. Germinal epithelium flat, tunica contains large light-staining cells, well differentiated from underlying cortex. Only a few primary follicles in the field; note large cell group in lower center.

Fig. 9.

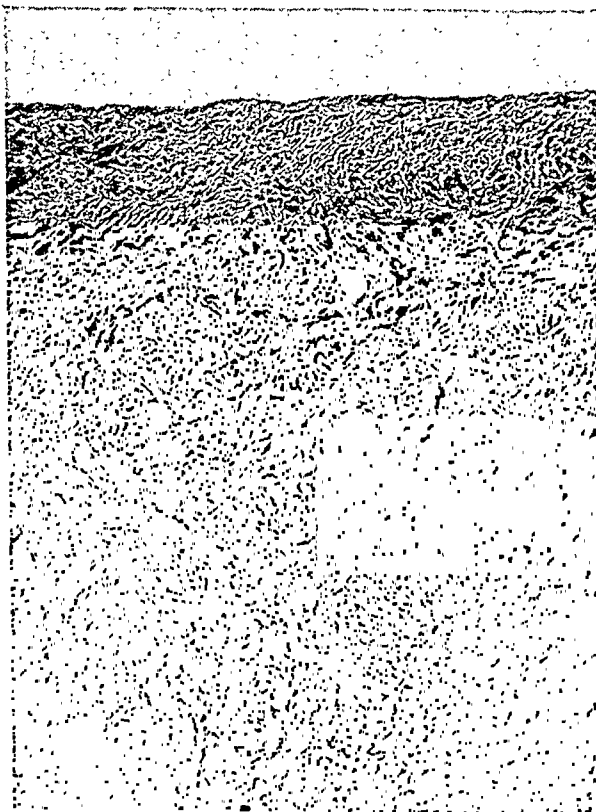


Fig.

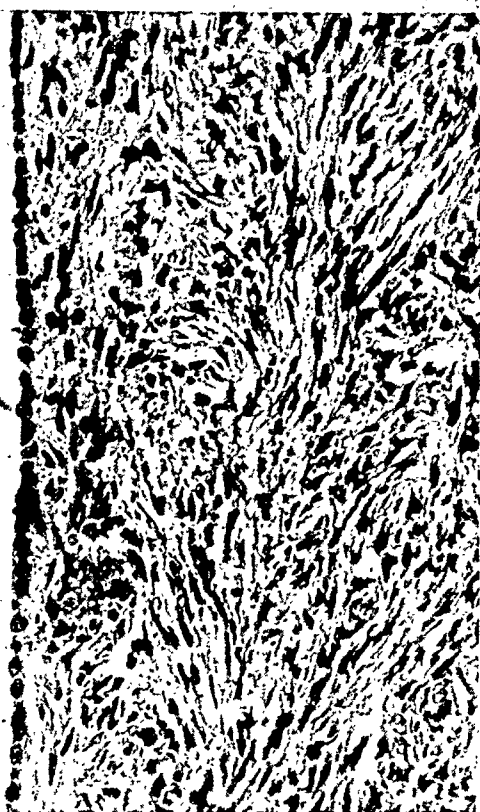


Fig. 11.

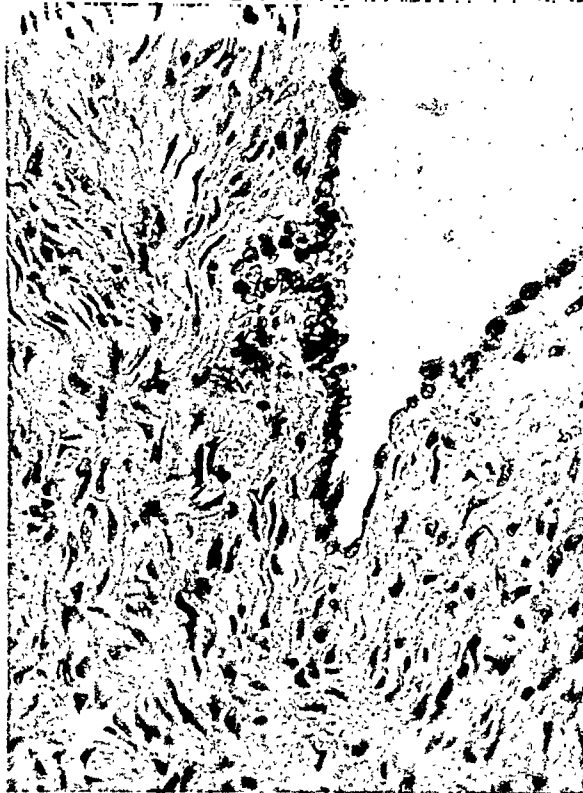


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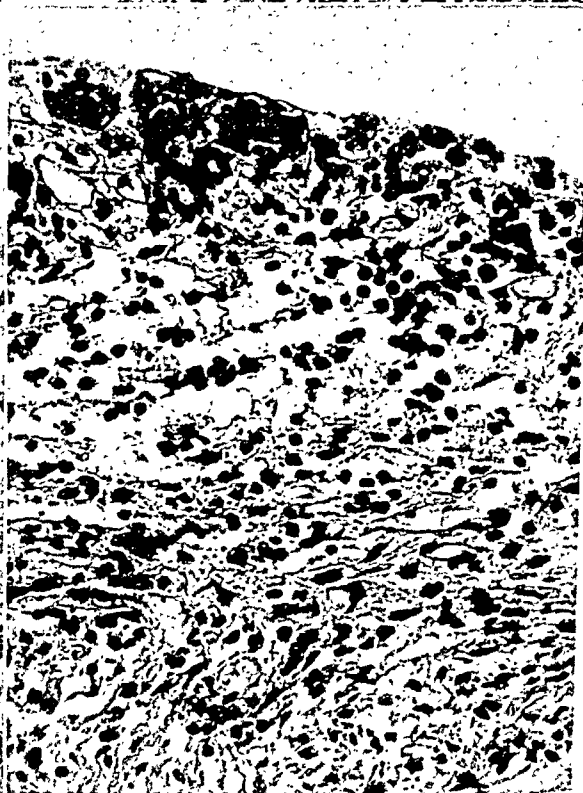


Fig. 9.—Ovary, 19 years old. Van Gieson stain, small amount of connective tissue in albuginea, black in picture. Note much lighter cortex, actually staining yellow like smooth tissue.

Fig. 10.—Ovary, age 24 years. Surface low cuboidal epithelium left, tunica and cortex as one not active. Fourth day of cycle.

Fig. 11.—Ovary, age 45 years. Active germinal epithelium with invasion of tunica albuginea.

Fig. 12.—Ovary, age 22 years. Surface showing marked germinal epithelial proliferation with invasion, showing ova in largest penetrating cell mass.

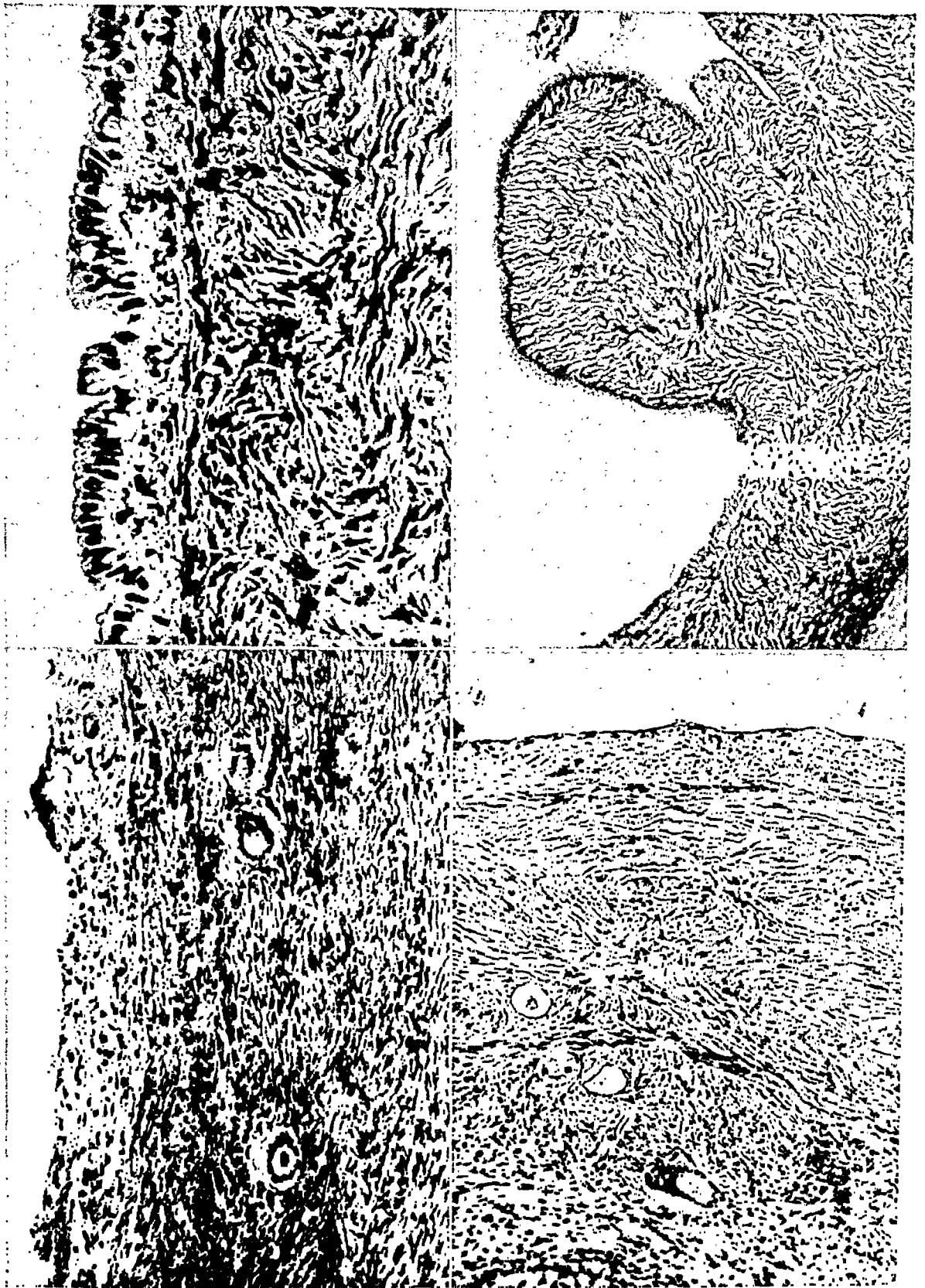


Fig. 13.—Ovary, age 28 years. Surface to left, marked activity of germinal epithelium with striking invasion of numerous cells in tunica albuginea. Differentiated ovum under epithelium in upper left of picture.

Fig. 14.—Ovary, age 45 years. Germinal epithelium fairly high, cortex and tunica as one, made up of diffusely scattered light-staining spindle cells.

Fig. 15.—Ovary, age 28 years. Tunica and cortex. Surface to left. Note ovum in middle of tunica. More advanced primary follicles in upper cortex. Tunica not very active. Germinal epithelium lost by artefact.

Fig. 16.—Ovary, age 21 years. Shows distinct active tunica, follicles penetrating deep in the cortex. Note deep cortical reaction about them, and also developing ovum at bottom of picture.

quently, we do not definitely now. It is frequently very difficult to determine whether cells are actually cells of the cortex per se or penetrating cells. We rather feel that the wandering cells become intermingled with the cortical cells and differentiation of these cells in many instances is not possible, chiefly due to similar intensity in staining reaction.

We believe that the idea of Simkins is quite possible. However, with the activity of the germinal epithelium and the tunica, along with the appearance of primary and primordial follicles in the tunica, which make their way into the deeper cortex, we are inclined to believe that the observations of Evans and Swezy meet the facts more directly. Conceding that new ova are formed which develop and become functioning after adolescence, it immediately places importance on the treatment of certain conditions with the use of the anterior pituitary preparations stimulating the ovarian follicular apparatus. This would involve cases of amenorrhea, sterility, and the anovulatory cycle. It would seem that, with the idea that the functional apparatus begins to show activity shortly after menstruation, reaching its maximum approximately a few days after ovulation, proper therapy and dosage would be most important, especially as regards intensity and timing. Accordingly, it might be reasonable to start the therapy in the middle of the actual menstruation, or before, continue rather vigorously for four or five days, and then gradually diminish it until about the tenth or eleventh day of the cycle.

### Conclusions

We feel from this review of our own material that the work of Evans and Swezy and Simkins concerning the development of the new ova after birth and in active adult life can be definitely accepted. So far as the origin of these cells is concerned, we conclude that they have their origin in the main from the germinal epithelium. The cortical source of these cells as suggested by Simkins cannot be discarded; this origin is more difficult to demonstrate. We believe both sources are quite possible, but this can be determined only by further special study of the cortex with this single point in mind.

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### Discussion

DR. JEAN PAUL PRATT, Detroit, Mich.—The story of the development of the definitive ovum is long and complicated. Since it is not possible to follow the process continuously in a single individual, the concept of ovogenesis is derived by piecing together fragments obtained from the study of many individuals and numerous species. Some phases are generally accepted while others are the subject of opposite opinions. Some anatomists and embryologists maintain that the earliest sexual cells are seen in the hindgut of early embryos from whence they migrate to the site of the future gonad. Here they are assumed to form or influence the formation of the future ovum. Others deny the existence of such migrating sexual cells. There is agreement, however, that the germinal



epithelium of the gonad is derived from the celomic epithelium. Furthermore, thousands of primordial follicles are formed during early intrauterine life. It has been accepted that most of the follicles degenerate at one time or another. Whether these follicles persist throughout the reproductive life and some of them mature with each menstrual cycle remains debatable. Also the time at which the formation of primordial follicles ceases has been variously placed at early embryonic life, throughout fetal life, the first year of post-natal life, up to puberty, and throughout the mature reproductive period.

Among early observers who published fragmentary evidence that ovogenesis occurred in adults may be mentioned: Pflüger (1863), Schron (1863), Koster (1868), Slavinski (1873), Wagener (1879), Van Benedin (1880), Amann (1899), Palladino (1898), Kingery (1917), Robinson (1918), and Arai (1920).

Edgar Allen (1922), having studied intensively the estrous cycle of mice, thought that they would be an excellent animal to observe for ovogenesis. He reasoned that the mouse has a greater fecundity than most other mammals; it has one of the shortest estrous cycles; the ovary is very small, facilitating complete examination, and the surface epithelium is well protected by a complete periovarian capsule. From Allen's observation on the ovaries of sexually mature mice he divided ovogenesis into three stages: (1) mitoses in the germinal epithelium, (2) small ova just under the germinal epithelium about which a few follicle cells are grouped, and (3) ova similar to the above but two cells below the surface of the ovary. The maximum incidence of the first stage was at estrus. Transition through the three stages required four to six days, i.e., one estrous cycle. Thus Allen established for the first time cyclic ovogenesis in sexually mature mammals.

In 1928, while Allen and I were examining human ovaries removed at the midmenstrual period, a search was made for mature follicles, early corpora lutea, and evidence of ovulation. The first stage of ovogenesis was observed occasionally. Evidence of the second and third stage was inconclusive. Compared with mice we found the study of human ovogenesis far more difficult because: (1) The number of ova developing in each cycle is less; (2) the human ovary is not so well protected, making it difficult to preserve the germinal epithelium intact; (3) the menstrual cycle is relatively long; and (4) the size of the ovary makes a complete examination laborious. The evidence we obtained was suggestive but we felt it was too meager to justify publication. The work of Evans and Swezy, to which Dr. Schwarz referred, is intriguing but not convincing so far as human ovogenesis is concerned.

A clear distinction should be made between ovogenesis on the one hand and follicular development through ovulation and corpus luteum formation on the other hand. The process of ovogenesis is inherent within the ovary and is not under control of the pituitary gland. The sequence of events seen in the formation of primordial follicles is probably brought about through the interaction of a self-contained system of organizers within the growing follicle. The nature of such organizers is not known but the existence of organizers is generally accepted. Only when follicles are developed to the antrum stage are they susceptible to the influence of the pituitary gland.

That the ovaries of young animals are refractory to gonadotropin is appreciated when selecting animals for pregnancy tests. Rabbits under 12 weeks or 1,200 Gm. are refractory. Rats and mice under 16 days are refractory. Even some older and larger animals are refractory.

Follicles above the antrum stage vary in their susceptibility to pituitary hormones. With a small dose only the large follicles respond. As the dose is increased the younger follicles respond but primordial follicles never respond. Hypophysectomy of adult animals is followed by atresia of all the follicles with antra and larger but the primordial follicles are not affected. The mammalian ovum may attain its full size in hypophysectomized animals. The absence of pituitary control over ovogenesis and early development of follicles is probably true of all vertebrates. We cannot hope to influence or control ovogenesis until we learn something of the nature of organizers.

The fragment of evidence that ovogenesis occurs in the germinal epithelium of the adult is a distinct contribution. I hope that Dr. Schwarz will continue his laborious efforts.



DR. EMIL NOVAK, Baltimore, Md.—Dr. Schwarz's paper represents a valuable contribution in a field in which there was clear need for further investigation. Since the publication of the paper of Evans and Swezy many years ago, based as it was on studies on lower animals, there has been almost no systematic effort to investigate human ovaries from the same viewpoint. Following the report of Evans and Swezy, I looked unsuccessfully for evidence of postnatal ovogenesis in the routine examination of ovaries, but a more intensive investigation is necessary before any conclusion can be drawn, and the present paper represents a study of this sort.

The question of ovogenesis is bound up with two other questions, concerning both of which there is still difference of opinion. First, there is the question of whether the germ cells have their origin in the so-called germinal epithelium of the ovary, or whether they migrate to the ovary by way of a *Keimbahn* from a much earlier situs in the primitive hindgut. The latter origin has been definitely established in certain lower animals, and the evidence for the existence of a *Keimbahn* in the human being is becoming increasingly strong.

The second question is as to whether the early sex cords and the Pflüger tubules are produced by invagination from the germinal epithelium, or whether, as now is accepted by most embryologists, these structures are formed by differentiation in situ from the ovarian mesenchyme, which would explain the origin and the histological and clinical characters of certain special ovarian tumors, as I have elsewhere discussed.

Whatever the original source of the germ cell may be, it may still be true that some degree of accessory ovogenesis may arise from the germinal epithelium. Gruenwald, incidentally, has described certain accessory sex cords arising from the surface epithelium, although he arrives at no definite conclusion as to their significance. Dr. Schwarz's slides are highly suggestive, but his own conclusions are still conservatively tentative, so that I hope he will continue his studies in this hitherto almost neglected field.

DR. ROBERT CREADICK, Durham, North Carolina.—Twelve years ago when I was a pupil of Dr. Edgar Allen we initiated a study as a principal *arbeit* on my part by experiments on rats, mice, and monkeys. Upon occasion I feel that the anthropoid apes are not so far below us. I think the application here might be well put. The alkaloid colchicine was employed, which has the capacity of arresting dividing cells in metaphase. It was almost as though we were using radioactive tracers on the immature female animals to find out which parts of the genital tissue responded. The stimuli used were Prephysin (APL) and pregnant mares' serum. The response was magnificent. I do, however, feel that the continuance of our studies was rather against Swezy and Evans' report.

Cyclic ovogenesis does occur and our control animals which were sacrificed showed practically no evidence of ovogenesis. Active mitosis did occur in the germinal epithelium of ovaries of the mature mouse at estrus. It seems to be a fundamental process.

DR. SCHWARZ (Closing).—Referring to the question that Dr. Pratt raised about mitosis in the ovary after birth, I personally did not see any evidence of mitosis nor did Swezy and Evans, but both Evans and Simkins studied minutely the nucleus of the ovum before birth and they found mitosis then.

After birth, the only other phases of further maturation are noted in the ovum at ovulation with the formation of the polar bodies and their extrusion so well shown by Pratt and his co-workers. Swezy and Evans and Simkins have pointed out that ova may divide, but by amitosis, and I have seen evidences of that in some of my sections where there develops a sort of dumbbell nucleus just as it is about to split in two.

## PERSPECTIVES IN PREMATURITY\*

### Physiological Approaches to an Obstetric Problem

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FOR the conventional obstetrician, prematurity poses three chief problems. First is recognition and treatment of premature labor; second is the immediate and ultimate care of the premature infant; and third is the real, compelling truth of the statistical aspect of the subject. Prematurity alone ranked as the ninth single cause of human death in the United States in 1945 and there is no reason to suppose that this situation is materially different today.

For the physiologist, there are likewise three major problems centering about the larger one of prematurity. These are: (1) the characteristics and control of uterine growth during pregnancy; (2) the provision for the nutrition of the fetus; and (3) the complex question of muscular power for emptying the uterus of its contents at term, and not before. Taken together, these factors comprise the principal elements of what we may call the physiologic process of uterine accommodation of the products of conception. At all times, these elements must be so interrelated and integrated that they provide a uterine environment suited to the needs of the embryo and fetus if it is to develop normally. What, then, are the elements of uterine accommodation?

#### Elements of Uterine Accommodation

When a fertilized ovum enters the uterus and becomes attached to the endometrium, it finds this tissue prepared structurally and functionally for nidation. The main features of this are generally known to medical men. Then a series of complex changes begins to unfold. These are so interrelated that, taken together, they provide room for the unborn until the end of gestation. The main features of these changes are not generally known to medical men, and most obstetricians are inadequately informed regarding them.

Uterine growth is the most obvious of these changes. The human uterus increases in size from an organ weighing about an ounce and one-half to one weighing over one and one-half pounds. While the uterus makes room for the unborn by extensive growth of tissues, it develops at the same time great contractile power. Normally, this remains dormant throughout most of pregnancy for a time which is fixed for each species. In this we witness the instructive spectacle of a growing force intended to overcome at a definitely future time a definite resistance, against which it never measures its strength until the actual moment of conflict has arrived.

Throughout this time, a continuous and adequate amount of maternal blood is supplied to the placenta in order to sustain the life of the unborn

\*Read before a joint meeting of the Denver Obstetrical and Gynecological Society and the Denver Pediatric Society, Denver, Colo., May 10, 1948.

child, and to provide abundantly for its growth. We may consider with profit, therefore, the salient characteristics of uterine growth during pregnancy, since this is the back-drop against which the drama of fetal development is played.

Uterine Growth and Uterine Accommodation

According to prevalent notions, the uterus accommodates the products of conception by progressive uterine growth from early pregnancy to its end. The view is generally—though erroneously—held that the uterus is able to grow almost indefinitely. Actually, we now know that there is a limit to the amount of growth taking place during pregnancy; that this is related to the degree and shape of the distending conceptus, and that the contractile power of the uterus at term is sufficient and little more to dilate the cervix during labor. The evidence for this is of the following sort.

The curve of uterine growth during pregnancy in the rabbit is shown in Fig. 1. The principal period of uterine enlargement occurs between the time of implantation and the twenty-fourth day of gestation (Reynolds, 1946). From this time until term there is little further uterine enlargement, yet this coincides with the time of most rapid fetal growth. This last phase, therefore, is a period of uterine stretching. Is this a generally applicable phenomenon?

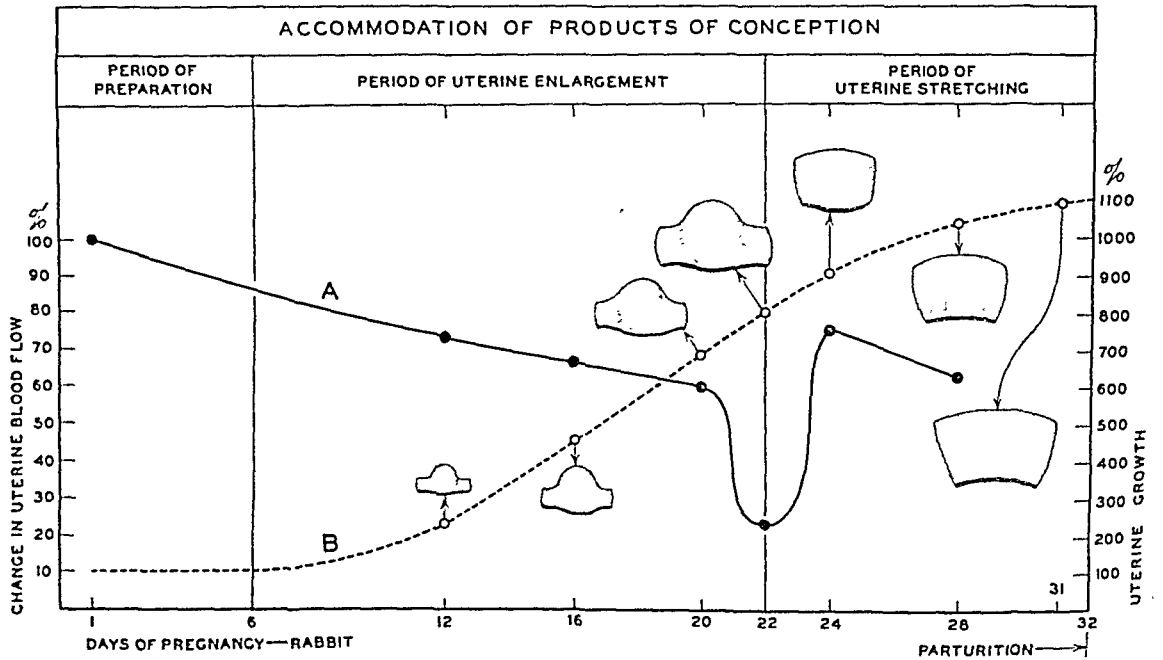


Fig. 1.—Uterine accommodation and circulation of blood through the uterus. Curve A, local blood flow through the lateral uterine vein in the uterine wall; B, increase in weight of the uterus during pregnancy, showing the relative size and shape of the conceptus at different times. See text for description. From AM. J. OBST. & GYNEC. 53: 901, 1947.

The limited evidence that we possess from various animal species suggests that it is. For example, in the rat and cow, data show that some limitation of uterine growth occurs toward the end of gestation, when the fetus is increasing most rapidly in size (Reynolds, 1940). Similarly, consideration of a few data from the human being and the rhesus monkey shows that the

pattern of uterine enlargement is rather like that of the rabbit (cf. Fig. 2; Reynolds, 1947). In short, we may say that in normal pregnancy, there comes a time when the size of the fetus becomes too large for its environment. That is the first aspect of uterine accommodation which is to be emphasized.

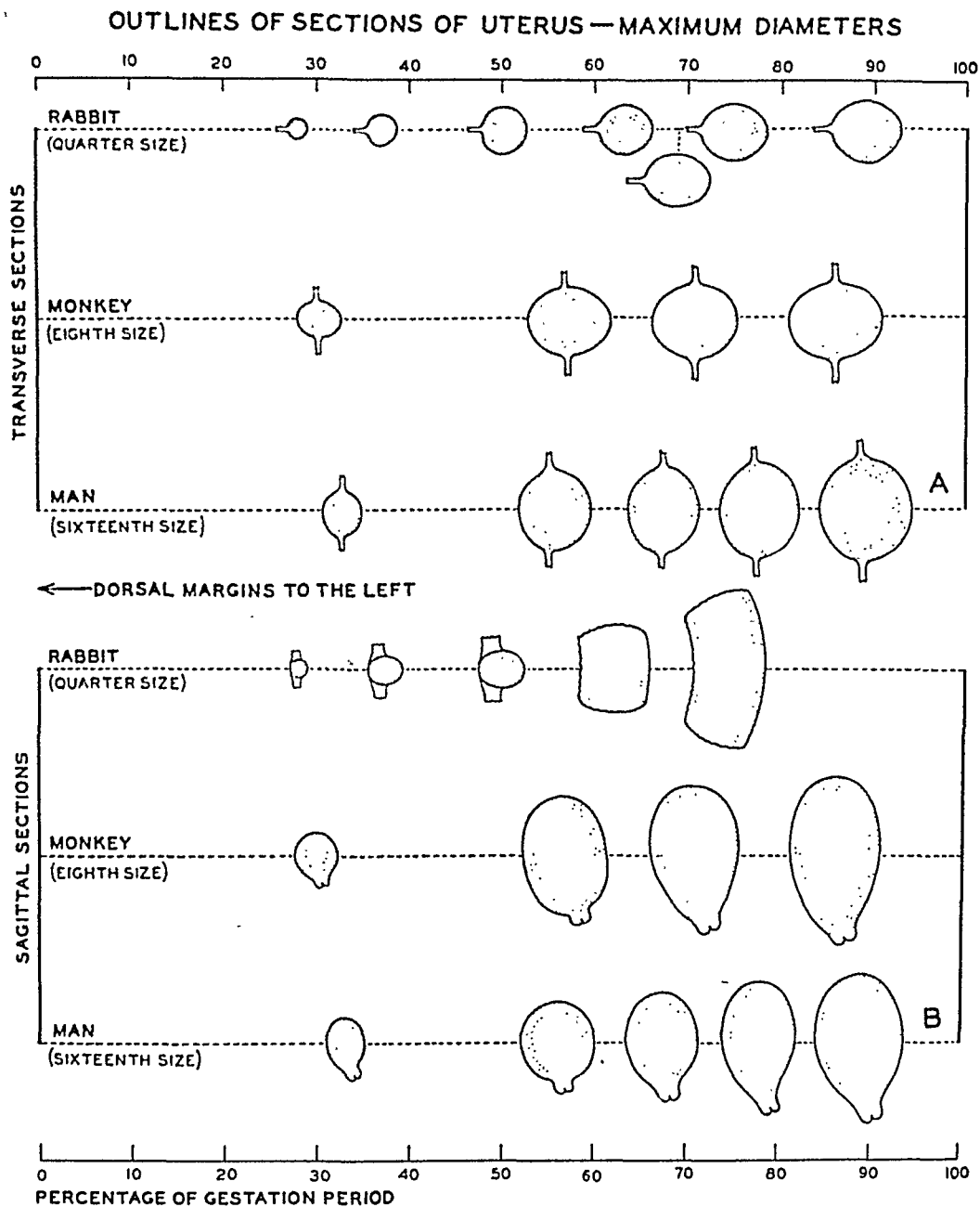


Fig. 2.—Diagrams showing the three-dimensional growth of the rabbit, monkey, and human uterus followed in the last part of pregnancy by a period of elongation. Top, cross-section, bottom, sagittal sections through the middle part of a conceptus. From AM. J. OBST. & GYNEC. 53: 901, 1947.

There is a second aspect of uterine growth that must be mentioned. In Figs. 1 and 2, it is shown that during the period of uterine enlargement the conceptus is spheroidal. During the period of uterine stretching, it is elongated and cylindrical in shape. Clearly, the *shape* of the uterus is a factor which plays a role in uterine accommodation along with uterine growth.

### Shape of the Conceptus and Uterine Accommodation

The shape of the uterus about a newly implanted conceptus is that of a small spheroid increasing rapidly in three dimensions. In the latter part of pregnancy in the rabbit, it is one of a cylinder, the size of which increases for the most part in but one dimension, namely, length (Reynolds, 1946).

This point is worth emphasizing for two reasons. First, the uterus behaves physically just like a hollow elastic membrane. Second, since the membrane is subjected to varying patterns of stress according to the predominant hormone influence at any time and the shape and size of the uterine contents, the resistance offered to the flow of maternal blood through it varies from time to time (Reynolds, 1947).

With respect to the first of these facts, the membranelike qualities of the uterus, our attention centers on the nature of the process of *conversion* from spheroid to cylinder. It has been established positively in the rabbit that this takes place within the space of a few hours (Reynolds, 1946). This means that the uterus is subjected to increasing tension until a critical condition develops. Then suddenly by changing shape the conceptus reduces the resistance to its growth imposed upon it by the spheroidal membrane which surrounds it on all sides with increasing tension, and it is then restricted in the cylindrical form by the confining action of the tissues of the uterus along its length. This situation is analogous to that of a long, sausage-shaped balloon blown with great force to a maximum spheroidal size near the mouth and then, when the internal pressure is sufficient, the balloon opens up with ease along its entire length. The pressure required to distend the elongating balloon immediately after conversion is then but a fraction of what is required to blow up the balloon when it was a sphere just prior to conversion. Physically, these relationships are approximately and in part as follows (Reynolds, 1946):

$$T_s = \frac{r^2 \cdot p}{2}$$

$$\text{and } T_l = \frac{r \cdot p}{2}$$

where  $T_s$  is the tension to be overcome by the pressure,  $p$ , in the sphere, and  $T_l$  is the tension to be overcome by the pressure,  $p$ , in the cylinder as it lengthens. The first is a geometric function of the radius, the second is a linear function of the radius. This means that, in the first instance, tension is proportional to the square of the radius, and in the second, it is directly proportional to the radius.

We see, therefore, that the growth of the conceptus during the period of greatest uterine growth is against increasing tension all around, whereas, during the period of rapid fetal growth and uterine stretching, the tension is reduced to a minimum. The mind must be peculiarly constructed which fails to see in this a marvelous provision of Nature to permit maximum fetal growth against the least possible obstacle in the latter part of gestation, and it is an excellent example of the Principle of Least Work in nature, in which work is accomplished at the lowest level of expenditure of energy possible.

The correctness of this interpretation has been proved in several ways but only one will be described here. In one set of experiments, the dye, Prussian blue, was injected into the uterine blood vessels under fixed conditions. This dye is freely diffusible, so if it enters the blood capillary vessels it should stain the surrounding tissues. It has been found (Reynolds, 1948) that until the twentieth day of pregnancy, the entire uterus is evenly injected

with the dye. On the twentieth and twenty-second days, the areas over the most distended regions of the uterus are not stained. Immediately after conversion there is again even penetration of the dye into all tissues, however distended they may be. Thus the conceptus changing shape by its own continued growth normally creates its own favorable environment for further growth, and this is by virtue of its change in shape. This *conversion* of the uterus from one form to another at a given point in pregnancy marks a physiological change of some moment in uterine accommodation.

### Conversion and Uterine Accommodation

Conversion takes place in all types of uteri. Fig. 2 shows that three-dimensional growth in the monkey and human being takes place about sixty-five per cent of the way through pregnancy. Recent work in collaboration with Dr. E. M. Ramsey by means of soft tissue x-rays and direct observation of the uterus in monkeys shows that conversion occurs somewhat, but not much, earlier than is indicated in Fig. 2.

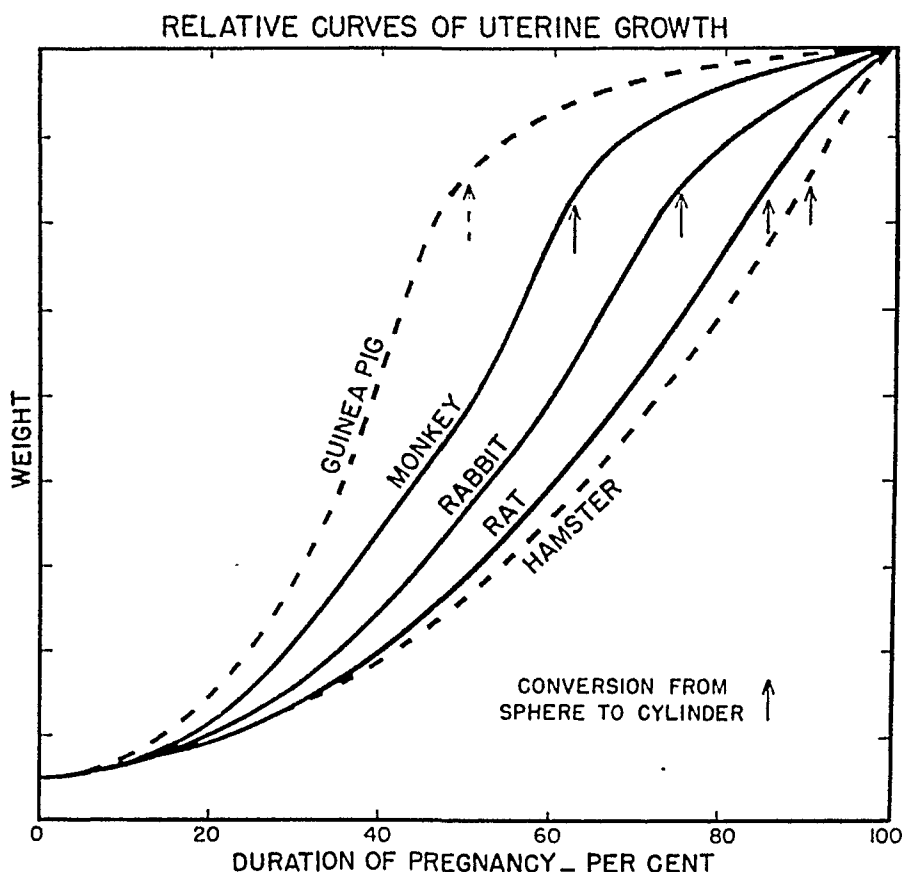


Fig. 3.—Schematic diagram of the relative curves of uterine growth in a group of widely divergent animal species. The time of conversion in each is indicated by the arrow. Dotted lines signify curves for which data are not yet adequately available. Observe that the earlier the time of conversion, the longer is the period of uterine stretching (i.e., relatively little uterine growth during the period of very rapid fetal growth).

Looked at another way, I have taken the liberty of plotting schematically in Fig. 3 the relative curves of uterine growth and the time of conversion in each from a number of widely divergent species. Additional observations will have to be made to increase and extend the precision of some of these curves. With these reservations in mind, the curves shown in Fig. 3 are of-

ferred tentatively to indicate the definitely established time of conversion in each species, and what appears to be the best evidence concerning the form of the uterine growth curve.

Here, the reader will see that the forms of the uterine growth curves are not the same for all species. The hamster and rat stand at one extreme; the monkey and the guinea pig at the other. The significant thing is that the earlier the time of conversion in gestation, the longer is the period of relatively little uterine growth. The significance of this will be clear from what has been said above: *the duration of the period of uterine stretching depends upon, and is proportional to the period of rapid growth of the fetus.* It marks, therefore, the beginning of accelerated fetal development, and *its occurrence should serve as an index of fetal maturity at birth.* More shall be said of this later, however.

### Fetal Maturity at Birth and Uterine Accommodation

The significance of the conclusion just stated is clear. If it is true that conversion may serve as an index of fetal maturity at birth, then we may postulate a relationship—in the terms of physiology of another day, a law—of fetal maturity at birth. It would rest upon the fact that fetal maturity at birth is proportional to the total duration of pregnancy which the fetus spends in an elongating uterus. What is the evidence that such a relationship may exist?

The evidence at hand is fragmentary and as yet incomplete. Much more must be learned before we can state it to be a fact. The data at hand are intriguingly suggestive, nevertheless. In the first place, the durations of pregnancy in the hamster, rat, rabbit, and guinea pig are, respectively, as follows: 15.5 days; 21 days; 32 days; 65 days. The proportions of pregnancy spent in a cylindrical uterus are, in the same order, 1/9th-1/10th for the hamster; 1/7th for the rat; 1/4th for the rabbit; about 1/2 for the guinea pig.

If one considers the maturity of the newborn of these species, one is impressed with the degrees of maturity which range from no sex differentiation of the external genitals in the hamster, to maturity in the guinea pig which includes temperature regulation, righting and postural reflexes, a coat of fur, and the ability to take food other than its mother's milk. At the present time, L. T. Bradin, a graduate student at Johns Hopkins University now working in the Carnegie Laboratory, is procuring systematic data on this subject by studying degrees of ossification before, at, and after birth in relation to the proportion of pregnancy the fetus has spent in the cylindrically shaped uterus. Enough is known to say now that a hamster about the fifth day after birth is comparable to a newborn rabbit in terms of ossification of the bones in the feet and equal to a 2-day-old rat. In other words, by adding some five postnatal days in the hamster to the one and one-half prenatal days in the cylinder, we find that the hamster on the fifth day after birth has lived about 31 per cent of its post-conceptual life in what may be called a "post-spheroidal" existence. The rabbit at a comparable stage of development (birth) has lived about 28 per cent of its post-conceptual life in a "post-spheroidal" existence and the rat, some 26 per cent. These relations are summarized in Table I.

Other data suggest the validity of a relationship between fetal maturity and the time of conversion also. The sensitivity of the newborn to anoxia is being used by Bradin to test it. It is a well-known fact that the less mature the newborn, the greater is its tolerance of anoxia, and vice versa.

TABLE I. COMPARATIVE MATURITY OF THE NEWBORN\*

CRITERION: EQUAL OSSIFICATION OF METATARSAL BONES				
COLUMN	FACTOR	HAMSTER	RAT	RABBIT
A	Duration of pregnancy, days	15.5	21	32
B	Days post partum	5	2	0
C	Conception age (A + B)	20.5	23	32
D	Conversion of conceptus, day	14	17	22-24
E	Days in cylindrical uterus	1.5	4	9
F	B + E	6.5	6	9
G	Per cent of gestation age post sphere	31.1%	26.0%	28.1%
$\frac{B + E}{C} \times 100$				

\*Bradin: Work in progress.

The data of Table II show the duration of respiratory effort in an atmosphere of nitrogen for the hamster, rat, cat, dog, rabbit, and guinea pig. Data on the time of conversion in these forms are available only in the case of the hamster, rat, rabbit, and guinea pig. It is clear that the immature hamster breathes much longer than the more mature rabbit. Some hamsters, in fact, have breathed for more than an hour in pure nitrogen. Much more work will have to be done, however, to establish the degree of correlation between these physiologic attributes of maturity and the time of conversion in the course of uterine accommodation.

TABLE II. RELATION OF UTERINE ENVIRONMENT TO ANOXIA TOLERANCE OF NEWBORN

SPECIES	DURATION OF PREGNANCY DAYS	PROPORTION OF PREGNANCY IN CYLINDRICAL UTERUS	SURVIVAL IN NITROGEN (MINUTES)	
			BRADIN*	HIMWICH ET AL.
Hamster	15.5	1/10-1/10	35+	
Rat				
Albino	21	1/4	15-20	50
Cotton†	27	—	11	
Cat	52	—		25
Dog	63	—		23
Rabbit	32	1/4	10	
Guinea pig†	63	ca. 1/2		7

\*Work in progress.

†Relatively mature at birth.

Another aspect of maturity which promises to lend itself to fruitful investigation is that of the development of reflexes. For example, the hamster and rat are devoid of postural (but not righting) reflexes at birth, whereas in the monkey and guinea pig these are well developed, in the latter rather more than in the former. This, too, compares qualitatively with the proportion of life spent in postspheroidal development.

There are two further points of comparative development to be mentioned which reveal that a maternal factor, not defined, controls the maturity and size of the fetus at birth. Many years ago the Dutch geneticist, Hagedorn, then of the University of California and now of Soesterberg, Netherlands, cross-bred wild hares with domestic rabbits. The offspring of the former are born with eyes open, a full coat of fur, possessing jumping and postural reflexes and the ability to eat food other than mother's milk. The duration of gestation is about fifty-six days. The appearance of the helpless



newborn rabbit is too well known to require comment here. The duration of pregnancy is thirty-two days. When a male hare is bred to a female domestic rabbit doe a most interesting physiologic phenomenon results. The young are born in thirty-two days in the same helpless immature state that newborn rabbit pups are.

A second evidence of maternal control of fetal size at birth is that reported by Walton and Hammond (1938) pertaining to the cross-breeding of large Shire horses and small Shetland ponies. Although the duration of pregnancy is not affected, it is found that the breeding of a Shire stallion to a Shetland mare results in offspring always of the same size as newborn Shetland ponies. In these two instances we witness evidence of some physiologic maternal mechanism which controls and determines the size, and hence the maturity, of the offspring at birth. I submit that there is no other known mechanism than that of uterine accommodation as outlined above by which these facts may be explained.

### Uterine Accommodation and Uterine Circulation of Maternal Blood

There are other aspects of uterine accommodation and prematurity which must be mentioned in a general discussion of fetal maturity.

The process of conversion brings about a favorable physical environment for fetal growth. How does this affect the circulation of maternal blood through the uterus?

Fig. 1 summarizes the results of experiments designed to test this point. By means of a standard physiologic technique, an estimate was made of the rate of blood flow through the tissues about the most distended parts of the uterus. One can see that progressive increase in the size of the conceptus is associated with an attendant decrease in blood flow until the time of conversion. Then there is a sudden, intense but transient decrease in the flow of blood through the uterine blood vessels. Following conversion with its attendant relief of tissue tension and opening up of smaller blood vessels, the rate of blood flow is restored to a level comparable to that seen earlier in pregnancy.

Why, one asks, is not the welfare of the fetus endangered at the time of this reduced uterine circulation? In some cases it is, for it is at this time that we begin to find resorbing fetuses in the latter part of pregnancy. Normally there are mechanisms which guard against this eventuality by virtue of a localized circulation to the placenta which is actually favored at the time the rest of the uterus experiences profound ischemia (Reynolds, 1948). The extent to which these facts apply to the *uterus simplex* of the primate is wholly unknown today.

### Uterine Contractility and Uterine Accommodation

In addition to the factors of uterine growth and fetal nutrition, the proper employment of the contractile powers of the uterus must be achieved in order to permit development of the fetus to full maturity, on one hand, and effective delivery at the time of parturition, on the other. We are just now in position to study these aspects of myometrial activity. An instrument for studying the patterns of activity of the entire uterus is now available (Reynolds, Heard, Bruns, and Hellman, 1948) and will be used to study uterine contractility in normal pregnancy and in its complications.

The characteristics of uterine contractions which are effective in dilating the cervix during labor are now known, and some of the attributes of ab-

normal patterns of uterine activity, in false labor, premature labor, and so forth, have been described (Reynolds, Bruns, and Hellman, 1948).

But knowledge of these patterns raises new and different problems to be investigated. For example, what hormonal and physical factors control normal and abnormal patterns of uterine activity? To what extent does the innervation control them? And finally, by what therapeutic means may premature and incoordinate activity of the uterus be controlled? Until answers are forthcoming to these and other questions, we may truly be said to be in the dark concerning the real role of uterine contractility as a contributing factor to prematurity.

### A Clinical Sign for Fetal Maturity?

With what practical point may the obstetrician concern himself, after the physiologist has indicated the avenues into which review of the problem of fetal maturity leads him? The cardinal fact which seems ripe for exploitation pertains to the relationship between conversion and subsequent fetal maturity at birth. We have seen that three-dimensional uterine growth ceases in the human being between six and seven tenths of the way through the course of pregnancy. If the obstetrician could know to within a week when this occurs, he would then know that every week after conversion is an added guarantee of full maturity and so viability of the baby at birth. His whole concept of the relation of fetal maturity at birth to the duration of pregnancy would be altered in the direction of certain knowledge in a matter which now entails what may be termed in the diplomatic language of World War I, "watchful waiting."

What the obstetrician needs is some concrete, palpable physical sign of conversion. What shall it be? Obviously uterine size is not suitable, since a small uterus may convert at a relatively earlier time than a large one and so give birth to a mature infant in a pregnancy of short duration. Shape of the uterus is the important thing. This presents difficulties in its estimation, particularly where three-dimensional growth must be considered.

It may be that a useful criterion of this will be found in one of the physical signs which is known to present itself in rabbits and in monkeys and so, probably, in women, too. It is that just prior to conversion the uterus is firm and tense; immediately after conversion it is loose, flabby, and soft. This is the result of the sudden diminution of uterine tension because of the change from a shape in which tension is a geometric function of the radius of curvature to one in which it is a linear function. The change is transient, however, since fetal growth will again take up the slack during the period of uterine stretching. This transient softening of the uterus, therefore, could be a clinical sign of first importance, if it is possible to judge this subjectively. But there no doubt are physical limitations to palpating the body of the uterus where the principal softening occurs. If this should be an impossible physical sign to employ, what others remain?

Clearly, this must be a matter for the obstetrician to decide. Perhaps during the sixth and seventh month abdominal profiles with the subject in a favorable position may reveal a characteristic change which is related to the process of conversion. Or again, uterine souffle, which now has no known physiologic or renal clinical significance, in some way may be found to betoken an alteration in hemodynamic conditions in the uterus which is related to the period of uterine stretching during the last part of pregnancy. If so, determination of the time of onset of some change in the character of uterine souffle

will serve auscultatory notice that uterine conversion is accomplished. And it will tell the obstetrician that from that time hence, each week of intrauterine life is a week toward viability.

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## SICKLE CELL ANEMIA AND PREGNANCY

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AT LEAST 33 cases of sickle cell anemia associated with pregnancy have been reported in the literature.<sup>1-20</sup> The maternal and fetal mortality figures may be summarized as follows:

Number of mothers	33	
Number of maternal deaths	7	(21 per cent)
Total number of pregnancies	73	
Total number of abortions	14	(19.1 per cent)
Total number of viable infants	59	
Number of infants surviving	50	
Deaths of viable infants	9	(15.2 per cent)
Total fetal loss in 73 pregnancies	23	(31.5 per cent)

The seven maternal deaths which have been reported in cases of sickle cell anemia associated with pregnancy are summarized in Table I. Infections, peripheral vascular collapse, thrombosis with embolic phenomena, and cardiac failure were the main causes of death. The clinical courses of three of the seven fatal cases were complicated by toxemia of pregnancy. In these fatal cases, as well as in many others in the total series, prenatal care was lacking, and in a few instances the patient received her first medical care when in moribund condition. This was illustrated in the case described by Lash<sup>2</sup> in which the patient had been in labor for fifty-two hours with a conjugata vera of 8 cm., and belated cesarean section was followed by death of the patient six hours later. The autopsy pointed toward a "shock" type of death.

The weights of the organs in the seven fatal cases were of special interest. Two patients had spleens weighing 20 and 35 Gm. as evidence of the atrophy which occurs with sickle cell anemia, while two other spleens were tremendously enlarged, weighing 740 and 960 Gm. each. The heart weights were also slightly over the average, weighing 379, 420 and 390 Gm.

The cases of Bauer<sup>21</sup> and Tomlinson<sup>22</sup> should be mentioned as possible cases to be included in this review, but because of controversial points were not incorporated in our tables. Tomlinson,<sup>22</sup> in a review of a large series of cases of sickle cell anemia, described the case of a 23-year-old British West Indian woman dying of postpartum septicemia, but the author himself raised the question as to whether sickle cell anemia played any role in the cause of death. This was also true in the case described by Bauer<sup>21</sup> of a 20-year-old Negro woman who died in the fifth month of pregnancy with the cause of death as pelvic thrombophlebitis, with multiple pulmonary infarcts and macrocytic anemia of pregnancy. Microscopic section of the spleen showed sickle cells in the reticulum and severe siderofibrosis. Whether this case should be classified as macrocytic anemia of pregnancy or as sickle cell anemia with pregnancy could not be decided by Bauer.<sup>21</sup> Numerous authors<sup>2, 4, 5, 7, 12, 15, 16</sup> have reported the presence of the sickling phenomenon in the infants born of these thirty-three mothers. Twenty-one infants have been examined and eleven (52.4 per cent) were found to be positive for the sickle cell trait.

TABLE I. SUMMARY OF THE LITERATURE OF DEATHS OCCURRING IN CASES OF SICKLE CELL ANEMIA ASSOCIATED WITH PREGNANCY

AUTHOR	AGE	CLINICAL COURSE	WEIGHTS OF ORGANS (GM.)				AUTOPSY CAUSE OF DEATH
			HEART	SPLEEN	LIVER	KIDNEYS	
Yater and Molinari (1931)	25	Died 3½ weeks after a spontaneous abortion (27th week) "Abdominal crisis"	379	35	2090	366	Sickle cell anemia; old infarcts of spleen and kidneys; hypertrophy and dilatation of heart; "abdominal crisis"
Lash <sup>2</sup> (1934)	21	Died 6 hours after cesarean section after prolonged labor, uterine inertia 52 hrs. with obstetrical conjugate 8 cm. and 3,225 Gm. infant. Entered hospital & hypertension	-	960	2420	330	Widespread dilatation and engorgement of capillaries of lungs, kidneys, liver, and spleen. (Post-operative shock.) Sickle cell anemia
Killingsworth and Wallace <sup>3</sup> (1936)	28	No data. Died 6 weeks postpartum	-	-	-	-	Puerperal infection
Page and Siltens (1939)	20	Died 22 hours after admission in 24th week of pregnancy. Diagnosis: bronchopneumonia	420	20	-	490	Pulmonary embolism with multiple infarcts of the lungs. Thrombophlebitis, pelvic veins. Siderofibrosis of the spleen
Kobak, Stein, and Daro <sup>9</sup> (1941)	22	Died 6 hours after delivery of a full-term infant. Treated for right lower lobe pneumonia	-	-	-	-	Sickle cell anemia. Marked hepatosplenomegaly. Atelectasis and passive congestion, lower lobe of left lung. Parenchymatous changes in heart
Noyes <sup>13</sup> (1946)	32	Died undelivered in 28th week of pregnancy. Elevated blood pressure 170/100 with silver wire changes in retina. Toxemia	390	740	2030	-	Sickle cell anemia. Right sided heart failure. Visceral congestion
Carangelo and Otts <sup>17</sup> (1947)	20	Died 12 hours after delivery in 36th week of pregnancy. Edema and blood pressure 140/75. Temperature 103° F.	-	225	2170	-	Bilateral renal abscesses and overwhelming kidney infection

### Present Study

As may be seen from the above review, previous experience with sickle cell anemia in pregnancy indicates that both the maternal and fetal prognosis is grave. Since our experience at the Johns Hopkins Hospital with sickle cell anemia associated with pregnancy—eleven cases with no maternal deaths—permits a more sanguine outlook than has hitherto been indicated, it seemed desirable to report our observations.

During the period from 1927 to 1947, eleven cases of sickle cell anemia associated with pregnancy have occurred on the obstetrical service of the Johns Hopkins Hospital. During this period, 14,256 Negro women were delivered in this hospital. This is an incidence of 1 in 1,296 pregnant Negro patients. Diggs, Ahmann, and Bibb<sup>23</sup> found that the incidence of the sickle cell trait was 7.3 per cent in 8,453 Negroes and that 1 in 40 Negroes with the sickle cell trait had active sickle cell anemia. From their data, approximately 1 in 552 nonpregnant Negroes would have sickle cell anemia and therefore our incidence of 1 in 1,296 pregnant Negro patients would lend some support to the generally accepted belief<sup>7</sup> that sickle cell anemia is associated with decreased fertility.

Our criteria for the diagnosis of sickle cell anemia have been the generally described ones of Wintrobe,<sup>24</sup> namely, marked anemia, evidence of red blood cell regeneration as shown by nucleated red blood cells in smears, elevated icteric index and jaundice with marked sickling of the red blood cells in carefully prepared sickling preparations. It should be re-emphasized that the single finding of "sickling" of red blood cells does not make the diagnosis of sickle cell anemia. In our eleven cases summarized in Table II, the diagnosis of sickle cell anemia was established on the following points:

1. Anemia, values usually under 50 per cent hemoglobin.
2. History, abdominal and joint pains, jaundice, weakness, dyspnea.
3. Examination, asthenic habitus, leg ulcers, cardiac enlargement with systolic murmur.
4. Sickling preparations, immediate sickling of the red blood corpuscles, with 80 per cent or more showing sickling after a twenty-four-hour period.
5. Icteric index, varied from 10 to 30.
6. Blood smears, reticulocytes, nucleated red blood cells frequently encountered in Wright's stain preparations of the blood.

Very little emphasis has been given to the association of syphilis and sickle cell anemia but for matter of record 7, or 63 per cent, of our cases either had positive serology or had been previously treated for syphilis. The significance of this observation cannot be determined. In all cases the diagnosis of sickle cell anemia was made during the prenatal period and in addition all cases were admitted to the hospital for treatment and study during their pregnancy. The average total hospital stay was 35 days, of which 23 were antepartum days and 12 postpartum days. The age of the patients was compatible with the previous literature in which only three of thirty-three cases occurred in women more than 30 years of age. Likewise, the parity of our patients was low since only seventeen pregnancies occurred in eleven mothers and only one mother had had a previous viable or full-term infant.

The prenatal course of the patients was not always tranquil. As may be seen in Fig. 1, the degree of anemia present in some cases was extreme, with four patients showing hemoglobin values under 40 per cent. Whole blood transfusions were given to ten of the eleven patients during the period of gestation and immediate puerperium. The average amount of blood administered in these ten cases was 2,650 c.c. and the average number of transfusions per patient was 5.2. In one case it was necessary to give nine transfusions over a period of

TABLE II. CASES OF SICKLE CELL ANEMIA AND PREGNANCY AT THE JOHNS HOPKINS HOSPITAL SINCE 1925

CASE	YEAR	AGE	PARA- GRAV.	Hb. %	DELIVERY	BLOOD LOSS C.C.	MATERNAL OUTCOME	FETAL WEIGHT (GM.)	FETAL OUTCOME	SICKLING IN BABY	REMARKS
1	1927	21	0-1	21	Spontaneous	900	Well at 6 weeks	1,150	Died of pre- maturity		Labor induced because of anemia and cerebral thrombosis
2	1928	21	0-1	26	Low forceps	150	Alive	3,165	Alive		No follow-up
3	1938	27	0-1	30	Hysterotomy, 18 weeks		Died 2 years post- partum	200	Abortion		Chronic glomerulonephritis
4	1939	18	0-2	35	Low forceps	100	Well at 4 years	2,560	Alive	Negative	Tubal ligation 38th day postpartum because of feeble-mindedness
5	1945	20	0-3	62	Spontaneous	25	Well 2 years later	2,860	Alive	Negative at 2½ years	Gross hematuria from hemorrhagic cystitis
6	1945	17	0-1	50	Spontaneous	300	Well 2½ years later	2,120	Alive	Negative at 2½ years	Severe pre-eclampsia
7	1946	29	0-1	55	Spontaneous	250	Well at 6 months	1,950	Died of pre- maturity		
8	1946	23	0-1	48	Spontaneous	50	Well at 1 year	2,560	Alive	Negative	
9	1947	20	0-1	60	Breech, spon- taneous	250	Well at 6 months	2,860	Alive	Negative at 3 months	
10	1947	23	0-1	62	Forceps rotation	500	Well at 6 months	3,370	Stillborn		Occipitoposterior position rotated to occipitoan- terior
11	1945	20	3-4	50	Spontaneous	100	Well at 2 years	2,940	Alive		Mild pre-eclampsia

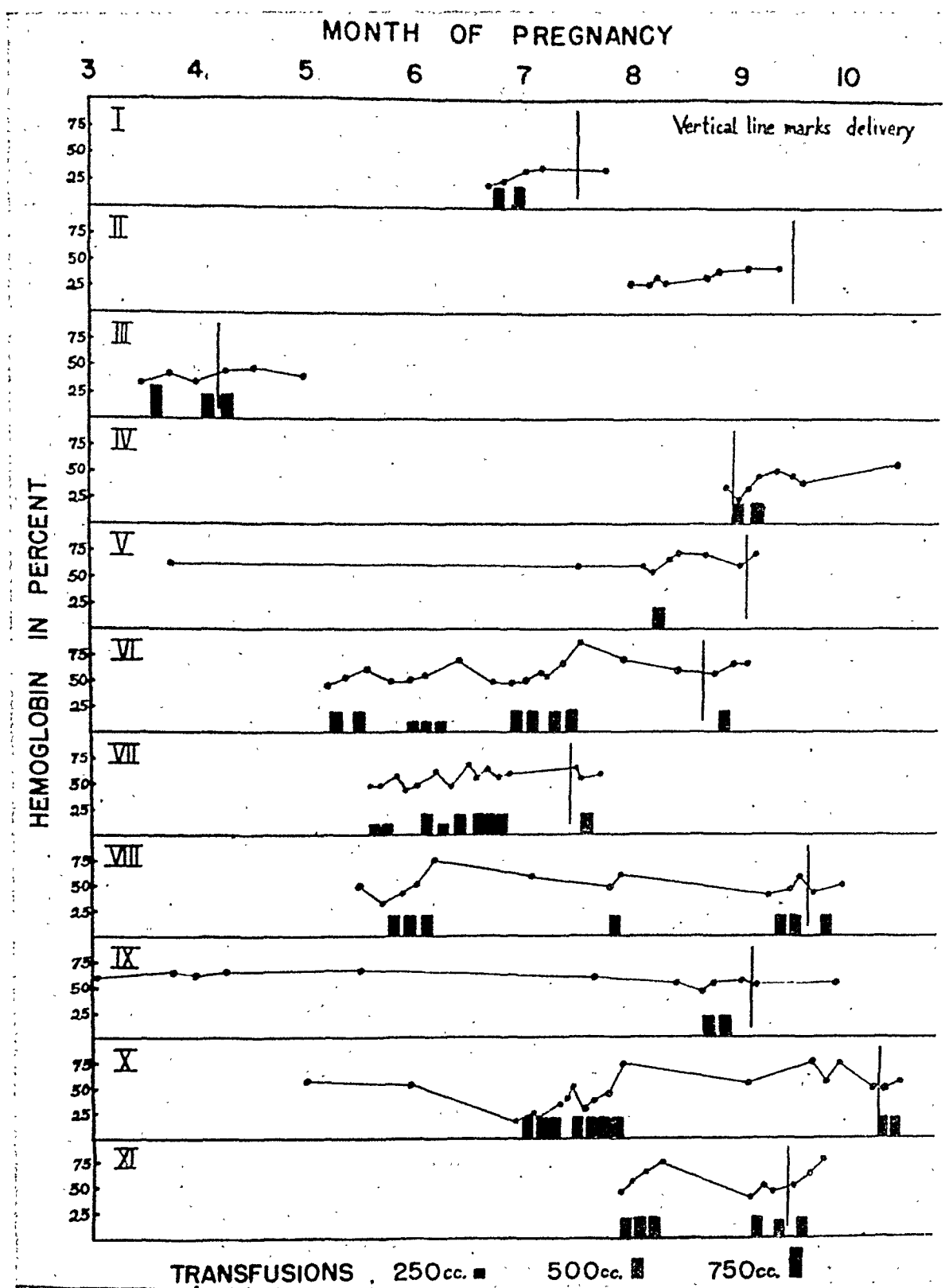


Fig. 1.—Hemoglobin values and blood transfusions administered to eleven cases of sickle cell anemia in pregnancy.



fourteen weeks in order to maintain the hemoglobin values at a satisfactory figure. In fifty-two transfusions recorded in Fig. 1, twelve transfusion reactions (23 per cent) occurred. Eleven of the reactions were the simple febrile reactions with chills and temperature rises to 101 to 102° F. within one to twenty-four hours after administration of the blood. One reaction was of a severe type accompanied by abdominal pain and hemoglobinuria. Practically all of the transfusion reactions were observed in three patients, one of the patients having five transfusion reactions. In several instances differences of opinion were expressed by members of the staff as to whether the reactions were abdominal "crises" or simple transfusion reactions.

Febrile reactions, independent of simple febrile transfusion reactions, developed during the prenatal and postpartum intervals in several of our patients. Pyelitis was present in three cases, meningitis in 1, and an unexplained febrile reaction in another, to make a total of five cases in which febrile reactions were present during the gestation period. Likewise, in the postpartum period, two cases of episiotomy infection, and single cases of brain abscess and pyelitis developed, which make a total of nine instances in which febrile reactions necessitated hospitalization and liberal treatment with bed rest, sulfonamides, and penicillin. In one patient, leg ulcers of considerable size were troublesome, requiring prolonged bed rest. The usual stasis edema of pregnancy adds to the delay in healing these ulcers.

### Hemolytic Crises

Hemolytic crises occurred in only one case during pregnancy (Case 9) and in three cases (Cases 3, 4, and 9) during the postpartum period. Although there is a wide variation in the frequency of "crises" in cases of sickle cell anemia, certainly one crisis during the period of gestation is a minimal number for eleven pregnancies.

Only one instance of a thrombotic process was observed. In this case a cerebral thrombosis took place similar to that seen in a pregnant woman described by Hodges and Bernstine<sup>16</sup> and to the observations in nonpregnant women by Hughes, Diggs, and Gillespie,<sup>25</sup> Connell,<sup>26</sup> and Bridgers.<sup>27</sup> This accident occurred in Case 1 two weeks before delivery. Because of anemia and cerebral thrombosis the labor was induced and a 1,150 Gm. infant was delivered, who died subsequently of prematurity. The mother survived the cerebral thrombosis and abscess and was well at the time of discharge from the hospital.

Three of our cases had mild to severe toxemias of pregnancy. The usual type of toxemia regime with bed rest, sedation and dietary control prevented serious complications. Hodges and Bernstine<sup>16</sup> observed that two of their three cases of sickle cell anemia associated with pregnancy developed signs and symptoms of toxemia of pregnancy. These authors feel that the arteriolar spasm of toxemia superimposed on vessels already partially occluded by the intimal proliferation which occurs in sickle cell anemia may bear an important relationship to the occurrence of signs and symptoms of thromboses, especially cerebral vascular blockage.

Complications during labor and delivery were minimal in our cases. Only one case of postpartum hemorrhage (900 c.c.) occurred, but blood transfusion eliminated any difficulty. The average length of the first stage of labor was fifteen hours and the average second stage was one hour and forty-five minutes. In view of the fact that most of our patients were primigravidas, these figures approach the normal; however, the average duration of the second stage was somewhat protracted and in one case was three hours long. The pelvic factor in these cases will be considered later.

We were able to study the placentas microscopically in only six of our cases. No abnormalities of fetal-placental weight ratios were observed. In two of the six placentas sickling of the red blood cells of the maternal blood was present (Fig. 2) but in no instance did we observe sickling of the fetal blood cells. Five of the eleven infants were also studied for sickling, but in no case was sickling demonstrable at the time of birth.

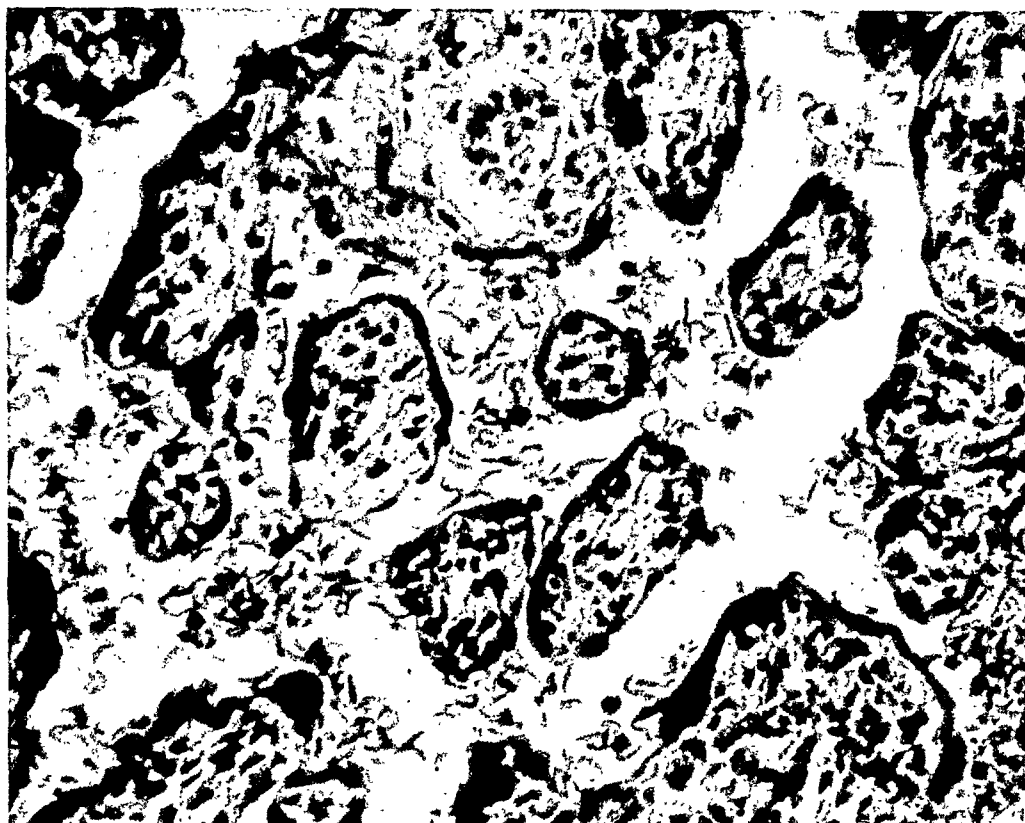


Fig. 2.—Placenta from Case 4 showing massive sickling of blood in the maternal sinuses. Note that the blood in the fetal vessels shows no evidence of sickling.

The fetal and maternal results are shown in Table II and summarized as follows:

Number of mothers	11	
Number of maternal deaths	0	(0 per cent)
Total number of pregnancies	17	
Total number of abortions	4	(23.5 per cent)
Total number of viable infants	13	
Number of infants surviving	10	
Deaths of viable infants	3	(23.1 per cent)
Total fetal loss in 17 pregnancies	7	(41.2 per cent)

The mortality rate of viable infants (over 1,000 Gm.) in our series (23.1 per cent) is not encouraging. However, closer analysis of Table II shows that in the three deaths of viable infants one case was due to induction of a small premature (Case 1) because of a severe cerebral thrombosis in the mother. The second death was in Case 7 which was associated with severe pre-eclampsia. The third death, the only one in a full-term infant, occurred after injudicious forceps

rotation in a type of pelvic architecture in which rotation is unwise. As also can be seen in Table II, not one of our patients died during pregnancy or the puerperium; however, one patient (Case 3) died two years after her pregnancy of chronic glomerulonephritis. To our knowledge (and with the exception of one case, postpartum follow-up at six weeks to four years was obtained on all our cases) this is the only death in the eleven cases.

Interesting features of the sickle cell anemia patient which should be of interest to the obstetrician are the changes in the bony structure and habitus of these patients. Winsor and Burch,<sup>28</sup> Sharp and Vonder Heide<sup>29</sup> have described these alterations in detail. They maintain that the sickle cell anemia habitus depends upon the extent and duration of the disease and the age of the patient at the time of onset. The sickle cell habitus was described as linear; the subjects were underweight, the hips and shoulders were narrow and the stature decreased. An increased upper dorsal kyphosis and lumbar lordosis and an increase in the anteroposterior diameter of the chest ("hoop chest") were characteristic with short trunks and roentgenologic evidence of flattening of the lumbar vertebrae. A few external measurements of the pelvis were made in these studies but no mention of the obstetrical capacity of the pelvis was included.

TABLE III. X-RAY PELVIMETRY IN FOUR CASES OF SICKLE CELL ANEMIA

CASE	INLET		MIDPELVIS			OUTLET		MORPHOLOGY	REMARKS
	O.C.	T.D.	I.S.	THOMS P. S.	A.P.	T.I.	P.S.		
5	11.0	11.0	9.3	4.6	12.2	9.0	8.3	Gynecoid-anthropoid	Convergent side walls. Straight sacrum
6	11.2	13.6	9.2	3.8	11.0	7.6	8.4	Gynecoid with anthropoid outlet	Convergent side walls. Straight sacrum
9	10.8	13.0	9.6	3.4	11.2	10.2	6.6	Gynecoid	Crests not united
10	12.3	12.9	9.2	4.0	11.6	9.6	5.3	Android-anthropoid	Straight sacrum. Convergent side walls

In view of the above observations, all patients who could be traced were measured. In three of 5 pelvises measured by clinical pelvimetry, outlet contraction was found to be present (intertuberous diameter of less than 8.0 cm.). In two other cases a diagonal conjugate of less than 11.5 cm. was discovered. Because of the known variations in estimation of obstetric capacity by clinical mensuration, x-ray pelvimetry was obtained on four patients and the data tabulated in Table III. From this table it will be noted that three of the four pelvises had convergent side walls, with heavy, blunted ischial spines. In Fig. 3, two of the pelvises have been illustrated with anteroposterior and lateral x-ray views to show the straight sacra with no forward rotation as is characteristic of kyphoscoliosis. The arches are narrow but not composed of heavy bony structure; otherwise they resemble the anthropoid type of pelvic architecture. Case 10 (Fig. 3) illustrates an instance in which a full-term infant was lost at the time of delivery by an ill-advised forceps rotation in a contracted outlet. Case 6 has a very small transverse diameter of the outlet (7.6 cm.) but fortunately the patient delivered a premature infant weighing only 2,120 grams. The type of pelvic architecture associated with sickle cell anemia habitus could very well be the reason for some of the difficult labors and prolonged second stage difficulties which are described in the previous literature.

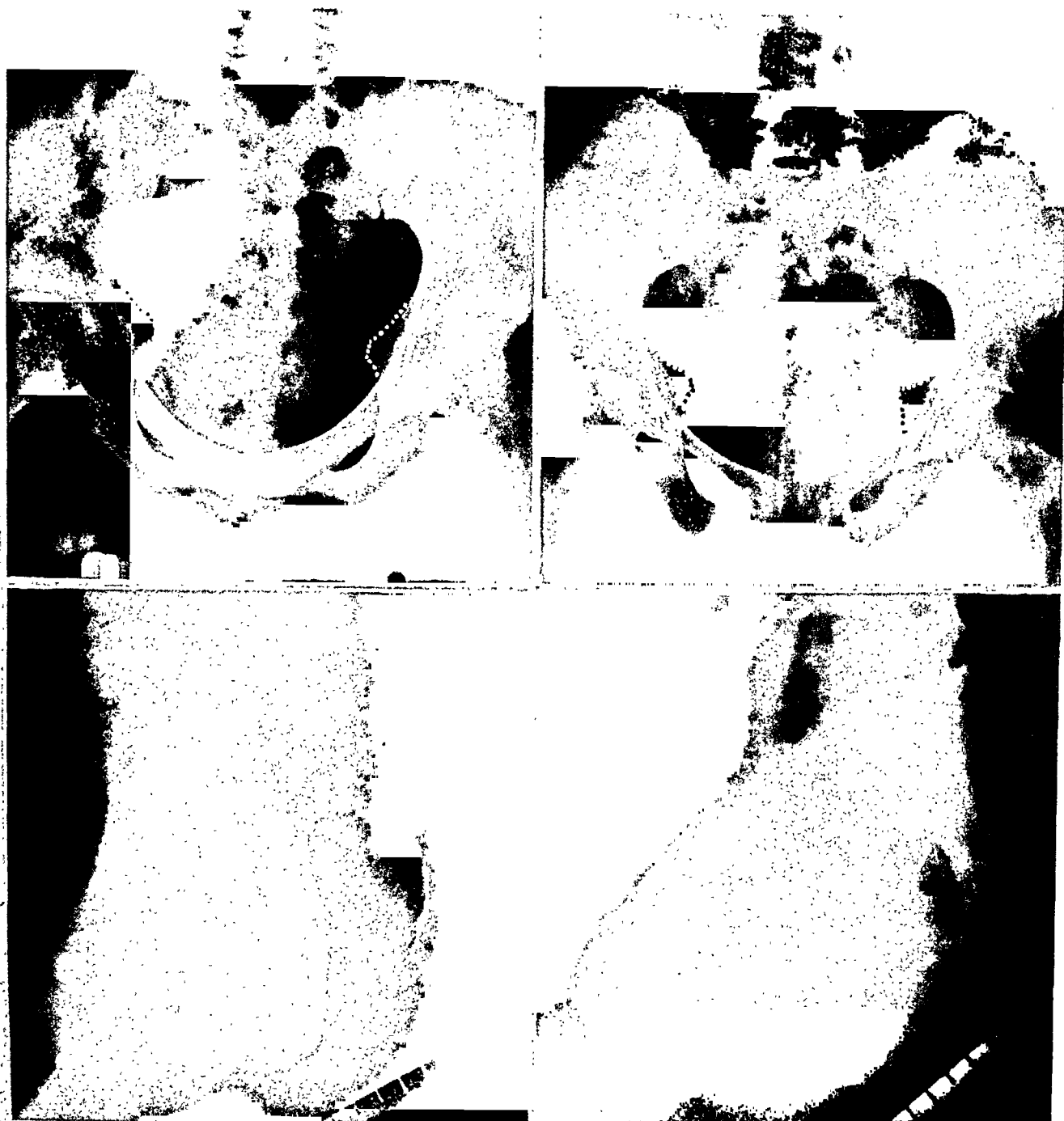


Fig. 3.—X-ray pelvimetry in Cases 10 and 6. On the left, an android-anthropoid pelvis of poor obstetrical type is demonstrated. On the right, a gynecoid pelvis with an anthropoid outlet and straight sacrum is shown.

### Treatment

The patients observed in the present study extend over a 20-year period (1927-1947). During this same interval, many new therapeutic developments such as antibacterial substances and blood transfusion have been added. Therefore, a plan of therapy should be outlined for cases of sickle cell anemia associated with pregnancy in the light of present knowledge and chemotherapeutic developments. Since the largest number of deaths from sickle cell

anemia both in pregnant and nonpregnant patients are due to intercurrent infections, cardiac and renal failure, shock and allied peripheral vascular changes, the treatment program should be directed primarily at the prevention of these accidents.

During the prenatal period sickle cell anemia patients should be observed frequently and if abdominal pains, febrile reaction, excessive weight gain, lowered hemoglobin values, hypertension, albuminuria, pyuria, or hematuria develops, the patient should be hospitalized immediately. Careful physical examination and hematological investigation should be performed. If fever is present, sources of infection should be sought and an attempt made to establish the bacteriologic etiology. Various combinations of penicillin or sulfonamide therapy should be instituted depending upon the sensitivity of bacterial organism in each individual case. During labor and the immediate puerperium it is wise to use penicillin in doses of 200,000 to 300,000 units. This step is advocated because of the high incidence of puerperal infection and morbidity, not only in cases of sickle cell anemia but also in all cases of anemia in pregnancy. Should early rupture of membranes occur, the prophylactic use of penicillin may be instrumental in protecting both mother and fetus from invasion by bacteria.

As has been previously discussed and illustrated in Fig. 1, we have used transfusions of whole blood liberally, with the average number of transfusions per case 5.2. Although the effect of the transfusions as measured by hemoglobin determinations is often temporary, certain beneficial effects appear to have been obtained rather than the mere increase in hemoglobin. It is true that the value of blood transfusions in sickle cell anemia patients in general has been debated. In nonpregnant patients, many authorities, such as Wintrobe,<sup>24</sup> consider them of little or no value. Bauer<sup>21</sup> and Tomlinson<sup>30</sup> have pointed out single instances in which transfusions may have had a deleterious role, while Tomlinson<sup>30</sup> has described the dangers that could be encountered if blood donors with sickle cell anemia are used. Except for the one patient in the present study, no such difficulties were observed.

To obstetricians, however, there may be other arguments in defense of the use of transfusions in the pregnant patient with sickle cell anemia. The presence of any type of anemia associated with gestation is a frequent precursor of future difficulties in the period of labor and the puerperium. Pastore<sup>31</sup> and Bickerstaff<sup>32</sup> have conclusively shown that puerperal morbidity is in direct proportion to the degree of anemia present in pregnant patients. As has been pointed out in the review of the literature, toxemias frequently accompany sickle cell anemia during pregnancy. The recent studies of Hinselmann,<sup>33</sup> Linzenmeier,<sup>34</sup> and Krogh<sup>35</sup> establish the basis for "stasis" within the fingernail capillaries of normally pregnant and toxemic patients. Knisely and Bloch<sup>36</sup> have made studies of intravascular agglutination occurring in normal, experimental, and pathologic states. One of the conditions in which they observed an increase in microscopic agglutination of red blood cells in venules and arterioles was sickle cell anemia. Recently, Odell and his co-workers<sup>37</sup> have found this "sludging" effect to be present in normal and pathologic pregnancy. Odell<sup>37</sup> also concludes that during shock sludge is related to subsequent hemodilution, or to the accompanying operative trauma rather than to an acute loss of blood. During infection, thrombophlebitis, and pre-eclampsia, the size of intravascular masses is particularly increased. What relationships do these alterations of pregnancy have in regard to the pathological physiology of sickle cell anemia?

The earlier workers with sickle cell anemia, such as Mason,<sup>38</sup> felt that hemolysis in sickle cell anemia was caused by phagocytosis of defective erythrocytes by macrophages with liberation of hemoglobin. Later on, Bauer<sup>39</sup> introduced the idea that simple mechanical impaction of masses of deformed red blood cells in small blood vessels was responsible for the hemolysis. Bauer<sup>39</sup> concluded

that the essential pathologic process in sickle cell disease was stagnation and conglutination of disfigured red blood cells with the resultant processes of thrombosis, ischemia with necrosis and fibrosis, and the resolution of red blood cells with the subsequent development of anemia. Recently, Ham and Castle<sup>40</sup> have developed the idea of an "erythrosthesis" which enhances hemolysis. These authors have observed that sickling blood has a higher viscosity which predisposes to erythrosthesis. Tomlinson,<sup>22</sup> in a study of eleven cases of nonpregnant "abdominal crises" which resulted in death, suggested that the mechanism of death was shock. His explanation of the shock was that the anoxia accompanying anemia was increased in sickle cell anemia because the sickled erythrocytes are poor carriers of oxygen to body tissues. The heart, as studied by Klinefelter,<sup>41</sup> is weakened in sickle cell anemia. The capillary anoxia results in plasma loss, hemoconcentration stagnation, and the stagnation removes available erythrocytes from the circulation, increasing the circulatory failure and anoxia, which perpetuates the vicious cycle of shock. Tomlinson,<sup>22</sup> therefore, feels that transfusions must be given in sickle cell anemia, particularly in the presence of "crises." In addition to the alterations of the maternal physiology which would enhance the difficulties in treatment of the anoxia of the mother, the exchange of oxygen between mother and fetus must be maintained. With these points in mind, transfusions would appear to be indicated in the mother with sickle cell anemia. It is also advisable to use sodium lactate solutions along with whole blood to prevent not only renal complications but possibly also to reduce the sickling tendency by raising the pH of the blood. Altmann<sup>42</sup> attempted to determine the fate of transfused erythrocytes in sickle cell anemia and concluded that the hemolytic process in sickle cell anemia affects only the patient's own red blood cells which are abnormal due to some hereditary factor, while the transfused cells remain unaffected.

Reinhard and his co-workers<sup>11</sup> have tried the effects of high concentrations of inspired oxygen on patients with sickle cell anemia. With the exception of a decrease in the degree of intravascular sickling of red blood cells, no consistent change in the rate of hemolysis occurred during the period of oxygen administration. Only minor toxic manifestations developed during the periods of oxygen therapy. Although no great benefits were derived from oxygen therapy, it should be pointed out that in patients with sickle cell anemia congestive heart failure which does not respond to digitalis has been reported by Klinefelter.<sup>41</sup> It may be necessary during pregnancy to use oxygen therapy since there is an increasing circulatory burden on the normal pregnant patient's heart, and this alteration on an already affected cardiac function in sickle cell anemia patients would be very serious. Therefore, the patients with sickle cell anemia with pregnancy should receive treatment closely resembling the type given patients with valvular heart disease.

The question of anesthesia is difficult, but the advent of various types of block anesthesia offers some advantage over inhalation anesthetics such as nitrous oxide and oxygen alone or combined with ether; this is particularly important in regard to the fetal outcome. Everything done to prevent circulatory stasis is advantageous in the treatment of patients with sickle cell anemia and pregnancy. Bauer<sup>39</sup> suggests sufficient muscular exercise, avoidance of prolonged bed rest, thyroid extract, cool baths, and saline and dextrose infusions to prevent circulatory stagnation.

In the previous discussion we have indicated our optimistic attitude that with appropriate medical and obstetrical care patients with sickle cell anemia can be safely carried through pregnancy. However, one of the problems confronting the obstetrician is the question of therapeutic abortion and sterilization in women afflicted with sickle cell anemia. Textbooks of hematology<sup>24, 38, 43</sup> state that sickle cell anemia is a hereditary disease transmitted as a Mendelian

dominant factor. Closer analysis of the literature as to the source of this conception shows that it apparently originated with Huck<sup>44</sup> and Sydenstricker.<sup>19</sup> Huck<sup>44</sup> studied two families for three generations and found that the "sickling" phenomenon is transmitted in this manner. His data and charts are only concerned with the sickling trait and therefore are insufficient evidence to conclude as he did, that sickle cell anemia is also hereditary. Mason<sup>38</sup> stated that proof of the statement that sickle cell anemia invariably precedes the development of sickle cell anemia is still a matter of debate. Lewis<sup>45</sup> also believes that the relationship of the disease sickle cell anemia to the sickle cell trait is a matter of controversy. It is important to point out that some authors like Murphy and Shapiro<sup>46</sup> feel that the anemia differs from the trait only in a matter of degree. This viewpoint is also shared by Bauer<sup>39</sup> who feels that the anemia is a secondary condition and that sickle cell anemia may be converted to active sickle cell disease by some acute infectious disease or surgical procedure. Even if one were to consider every person with the sickling trait a potential case of sickle cell anemia, the figures of Diggs et al.<sup>23</sup> would indicate that only one in forty patients with the trait develops anemia. Apparently no way has been devised to predict the cases of sickle cell anemia which will develop the acute phase of the disease.

As yet the prognosis of children born to mothers with active sickle cell anemia cannot be stated with assurance. A thorough search of the literature revealed only two reports (Killingsworth and Wallace<sup>5</sup> and Corrigan and Schiller<sup>20</sup>) in which the true picture of sickle cell anemia has been observed in both the mother and her children. Until more data have been accumulated, conclusions cannot be made as to whether an infant born of a mother with sickle cell anemia is more likely to develop this disease than an infant born of a mother with only the sickling trait. Therefore, therapeutic abortion for sickle cell anemia alone would not be justified. Sterilization will rarely be necessary since patients with sickle cell anemia have an average number of only two pregnancies and some 20 per cent of the pregnancies terminate in abortion. However, many other factors may govern these recommendations. Bauer<sup>39</sup> has advanced the idea that patients with sickle cell anemia belong to a group characterized by constitutional degenerative stigmas which he designates as the "status degenerativus." From the reports in the literature the clinician must be on guard against many treacherous and peculiar mechanisms which initiate "sudden death" in patients with sickle cell disease. Each case must be given individual consideration. For instance, an associated toxemia of pregnancy with sickle cell anemia could alter one's decision regarding interruption of pregnancy and future childbearing.

### Discussion

The high maternal mortality rate of 21 per cent reported in the previous literature could not be corroborated in the present study of eleven cases of sickle cell anemia associated with pregnancy observed in the Obstetrical Department of the Johns Hopkins Hospital over a 20-year period (1927-1947). All patients survived the period of the pregnancy and puerperium. Follow-up on the patients extended from six weeks to four years in the present study. In Table IV, a summary of the previous literature, the present study, and the combined total of forty-four cases are presented. From these data the total fetal loss and abortions appear to be increased over normal. Our percentage of deaths of viable infants (over 1,000 Gm.), 23.1 per cent, is higher than the figure of the previous literature, 15.8 per cent, but two of the deaths in the present study and some of the reported fetal deaths suggest ill-advised obstetric and pediatric procedures.

With improved methods, there is every reason to believe that a fetal mortality rate of 5 to 10 per cent may be attained.

TABLE IV. SUMMARY OF MATERNAL AND FETAL MORTALITY OF CASES OF SICKLE CELL ANEMIA IN THE LITERATURE AND IN THE PRESENT STUDY

	PREVIOUS LITERATURE		AUTHORS' CASES		TOTAL CASES	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Number of mothers	33		11		44	
Number of maternal deaths	7	21.0	0	0	7	15.9
Total number of pregnancies	73		17		90	
Total number of abortions	14	19.1	4	23.5	18	20.0
Total number of viable infants	59		13		72	
Total number of surviving infants	50		10		60	
Deaths of viable infants	9	15.2	3	23.1	12	16.6
Total fetal loss	23	31.5	7	41.2	30	33.3

Sickle cell anemia should be looked for in obstetrical services handling Negro patients. Practically all of our cases had the diagnosis of this disease established while under the care of the obstetrical staff. Therefore, the routine testing of Negro patients for hemoglobin values followed by sickle cell diagnostic tests should be a part of the function of the prenatal clinic. Blood donors probably should also be checked for sickle cell anemia as suggested by Tomlinson.<sup>30</sup> It is often stated that sickle cell anemia is easily diagnosed but in the present study three cases, which had been recorded in the files as sickle cell anemia, had to be rejected because insufficient evidence was present to establish clearly this diagnosis. None of these patients died and only the sickling trait was present with moderate anemia. One patient had tuberculosis, another rheumatic fever, and a third chronic pyelonephritis.

### Summary

The present study is a review of eleven cases of sickle cell anemia associated with pregnancy observed on the Obstetrical Service of the Johns Hopkins Hospital over a 20-year period (1927-1947). No deaths occurred in these eleven mothers during the period of the pregnancy or puerperium. Three of thirteen viable infants died, giving a fetal mortality of 23.1 per cent. These figures justify a more optimistic outlook than hitherto noted in sickle cell anemia associated with pregnancy, since the previous literature reports an average maternal mortality rate of 21 per cent in thirty-three cases. Fifty-nine viable infants were born of these thirty-three mothers with nine deaths, giving a fetal mortality rate of 15.2 per cent.

Sickle cell anemia occurred in one in 1,296 pregnant Negro women. Repeated hospitalization during the prenatal period was necessary. The average number of transfusions per patient during the pregnancy and puerperium was 5.2. Twelve reactions occurred in fifty-two transfusions given these patients (23.0 per cent). Only single instances of thrombosis and abdominal crises were observed during the pregnancies. Three cases were complicated by toxemias of pregnancy. Analysis of eleven cases did not support the idea that pregnancy exerted an untoward effect on the disease of sickle cell anemia.



X-ray pelvimetry was studied in four cases, of which three had convergent side walls with heavy, blunted ischial spines. The pelves revealed a tendency toward funneling and anthropoid architecture with straight sacra and narrow subpubic arches. Further x-ray studies should be made.

The treatment of sickle cell anemia associated with pregnancy demands constant medical observation and frequent hospitalization for investigation and treatment of concurrent toxemias and febrile states. Liberal use of penicillin, sulfonamides, and blood transfusions is needed to reduce both the maternal and fetal mortality rates. With the addition of the present study to the thirty-three previously reported cases in the literature, a total of forty-four cases have been observed up to the present time. Seven maternal deaths (or 15.9 per cent) have occurred with a fetal mortality of 16.6 per cent and a total fetal loss of 33 per cent. Therapeutic abortion and sterilization are seldom indicated in patients with sickle cell anemia associated with pregnancy.

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# THE EFFECT OF VERATRUM VIRIDE ON THE URINE VOLUME, BLOOD PRESSURE AND PULSE RATE IN NORMAL AND TOXEMIC PREGNANCY\*

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DURING the last few years a new surge of interest in the treatment of the toxemias of pregnancy with veratrum viride has appeared in the literature. Bryant<sup>1</sup> and Bryant and Fleming<sup>2</sup> were the first among modern authors to report a significant series of cases of eclampsia treated by this drug with successful results and low maternal mortality. Garber and Assali<sup>3</sup> added 40 cases to the series of Bryant and Fleming, making a total of 160 eclamptic patients treated at the Cincinnati General Hospital with the same regimen, resulting in a gross maternal mortality rate of 1.8 per cent.† Kellogg<sup>4, 5</sup> and Irving<sup>6</sup> reported a decrease from 25 per cent to 12 per cent in their maternal mortality in eclampsia following the institution of veratrum viride therapy.

Willson<sup>7, 8</sup> published a series of cases of pre-eclampsia and hypertensive pregnancy wherein he found a decrease in the urinary output following the use of veratrum viride. He concluded that this drug should not be used in the treatment of eclampsia and pre-eclampsia because there was no necessity for lowering the blood pressure in these conditions. He postulated that the existing hypertension was actually beneficial for the maintenance of normal kidney function.

This is at variance with opinions expressed by Hertig<sup>9</sup> and others<sup>10-11</sup> who state that the predominant element in the toxemias of pregnancy is a generalized vasospasm, with resulting capillary anoxia and tissue necrosis.

Impressed by Willson's report, we initiated a clinico-experimental work designed to evaluate the action of veratrum viride on the urinary output of normal, toxemic, and hypertensive pregnancies. Blood pressure and pulse rate were also recorded in order to evaluate any possible correlation between these two factors and the urine volume. The results form the subject of this paper.

## Material

Eight pre-eclamptic, two eclamptic, 3 hypertensive, and four normal pregnant patients comprised the present series. The duration of pregnancy varied from thirty-two weeks to full term. All of the patients were admitted to the hospital, kept at absolute bed rest, and placed on a 0.9 Gm. sodium chloride diet during the entire period of the experiment. Patients who were in active labor were eliminated because of the variation in blood pressure, pulse rate, and urinary output produced by labor pains. Of the eight cases of pre-eclampsia, six were severe and two mild. The diagnosis of pre-eclampsia was based on the presence of albuminuria, hypertension, edema, and subjective symptoms in the last trimester of pregnancy. One hypertensive, one eclamptic, and two pre-eclamptic patients were studied in the prepartum and postpartum period.

\*Veratrum viride was employed in the form of Veratrone, Parke, Davis and Co.

†Since this last report, there have been 21 more eclamptic patients treated, a total of 181 cases with one maternal death from eclampsia per se and two from sepsis.

### Method

Following admission, all patients were weighed and an indwelling Foley catheter inserted into the bladder; the first urine sample was discarded. The catheter was opened, thereafter, at hourly intervals and the bladder emptied completely each time. The present study was divided into three periods:

a. A control period varying from 8 to 48 hours. During this time the patient received measured amounts of water orally (100 to 400 c.c.). The urinary output, blood pressure, and pulse rate were recorded.

b. The period of veratrum viride administration, varying from 12 to 48 hours. It followed the control period immediately and consisted of the addition of subcutaneous doses of veratrum viride (0.2 to 0.7 c.c.) every two hours.

c. A combined period in which magnesium sulfate (50 per cent intramuscularly and glucose solution (5 per cent in distilled water) intravenously were added to the veratrum viride treatment.

This last method was applied to five pre-eclamptic and two eclamptic patients and it represented the treatment followed for more than twenty years in this hospital. In all of the periods intake, output, pulse rate, and blood pressure were recorded hourly or every two hours by the same observers to eliminate errors from personal variation. Since vomiting occurred frequently with large doses of veratrum viride, it was charted separately but was not included in the calculation of urinary output. Profuse sweating was observed frequently with large doses of this drug. It constituted, to a certain degree, a cause of error which could not be entirely avoided in calculating the output. To eliminate bed rest alone as a factor influencing diuresis and blood pressure, one pre-eclamptic and one hypertensive patient were studied in control periods alternating with veratrum viride. Urea clearance tests were performed at the end of each period using the Van Slyke method on three hourly specimens of urine and one of blood. Weight determinations were also recorded at the end of each period.

### Results

A. *Normal Pregnancy*.—All of the four cases responded in the same manner to the administration of veratrum viride. With doses varying from 0.2 to 0.7 c.c.—the usual effective dose in treating pre-eclamptic patients—there was practically no change in the urine volume, blood pressure, or pulse rate. The urinary output maintained the same proportion during the control and veratrum viride administration periods (Fig. 1). Fig. 2 illustrates an individual example.

B. *Toxemias of Pregnancy*.—Under this heading were included the patients with pre-eclampsia and those with essential hypertension not showing any sign of superimposed toxemia.

1. *Urinary output*: In almost all of these patients, a decrease in the hourly urinary output (vomiting excluded) varying from 15 to 60 per cent was observed following the administration of veratrum viride. The mean decrease for the entire group was 37 per cent. The maximum drop in output occurred when larger doses (0.5 to 0.7 c.c.) were given and lasted for approximately two hours. It coincided with the sudden fall in blood pressure, profuse vomiting, and diaphoresis. However, with the return of the blood pressure to a desired level (circa 140/90) which was always lower than the control level, the urine volume increased and was so maintained even though the administration of veratrum viride was continued. Because of the compensatory polyuria which was observed frequently after the initial decrease in output, the total urinary output for the control and veratrum viride periods maintained almost similar proportions in all of the patients (Figs. 3, 4, and 5). The patients who were studied under the

combined regimen invariably showed increased urine volume despite the fact that the blood pressure and pulse rate were lower than in the control and veratrum viride periods (Fig. 4). The patients who were studied in the postpartum period had a marked diuresis in both control and veratrum viride

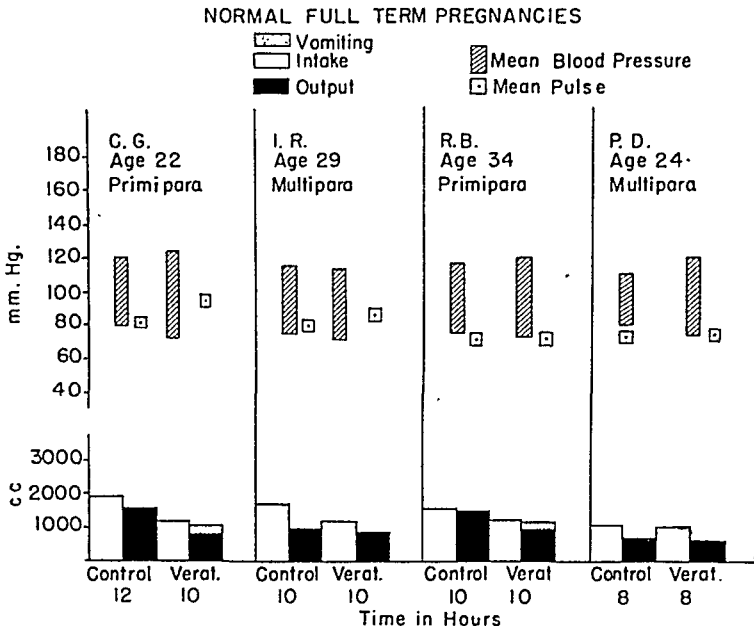


Fig. 1.—Total intake and output, mean blood pressure and pulse rate of four normal full-term pregnancies.

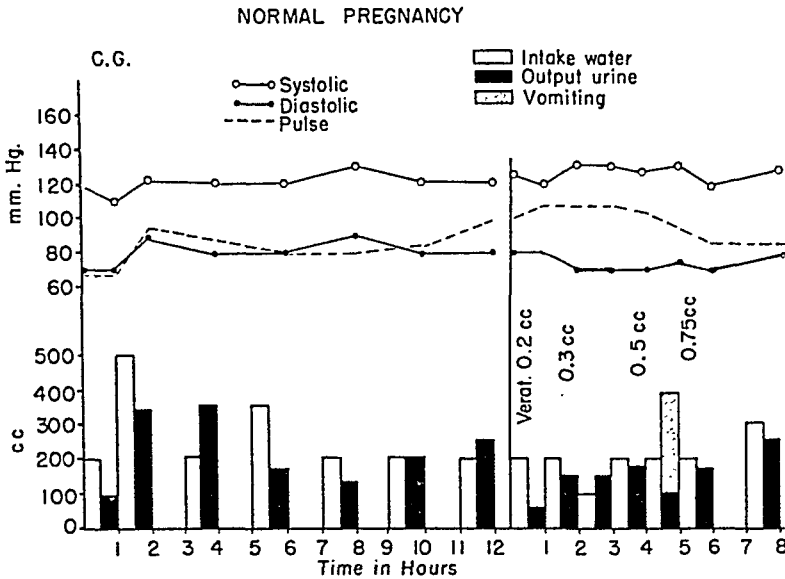


Fig. 2.—Blood pressure, pulse rate, intake and output of a normal full-term pregnancy in control and veratrum viride periods.

periods. Two patients were studied according to the alternating method mentioned above. In the prepartum, one of them (Fig. 6) showed a transitory decrease in urine volume each time veratrum viride was given in 0.7 c.c. doses. The other (Fig. 7) did not show any alteration. In the postpartum, both had profuse diuresis.

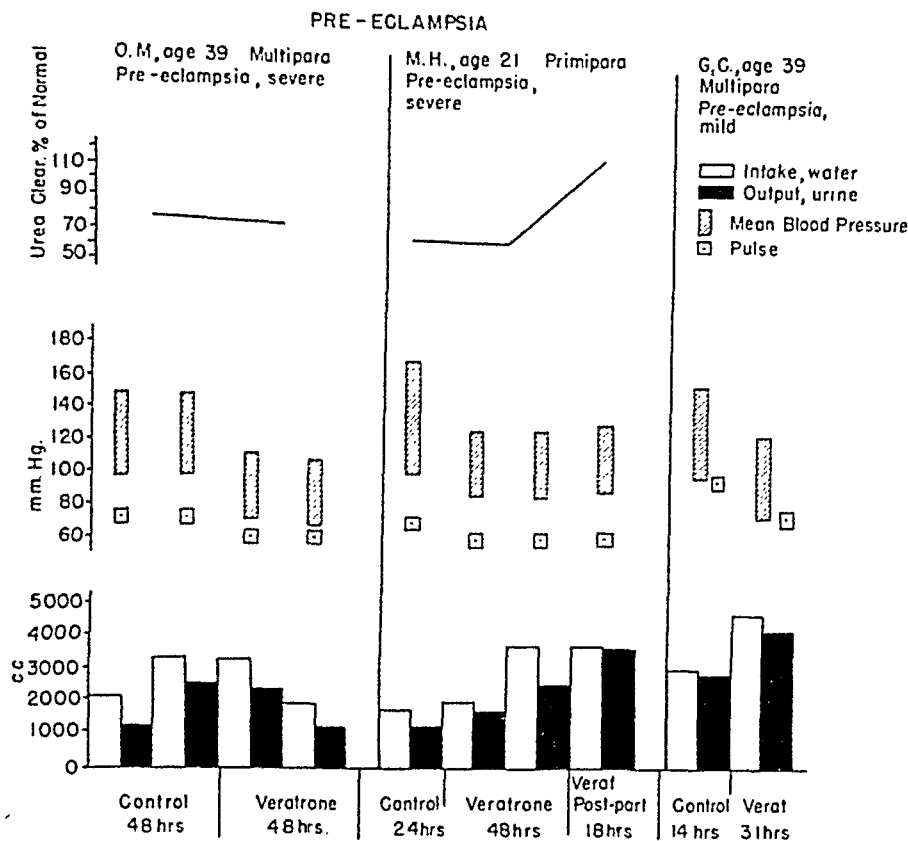


Fig. 3.—Total intake and output, mean blood pressure and pulse rate, and urea clearance of three pre-eclamptic patients studied on control and veratrum viride periods.

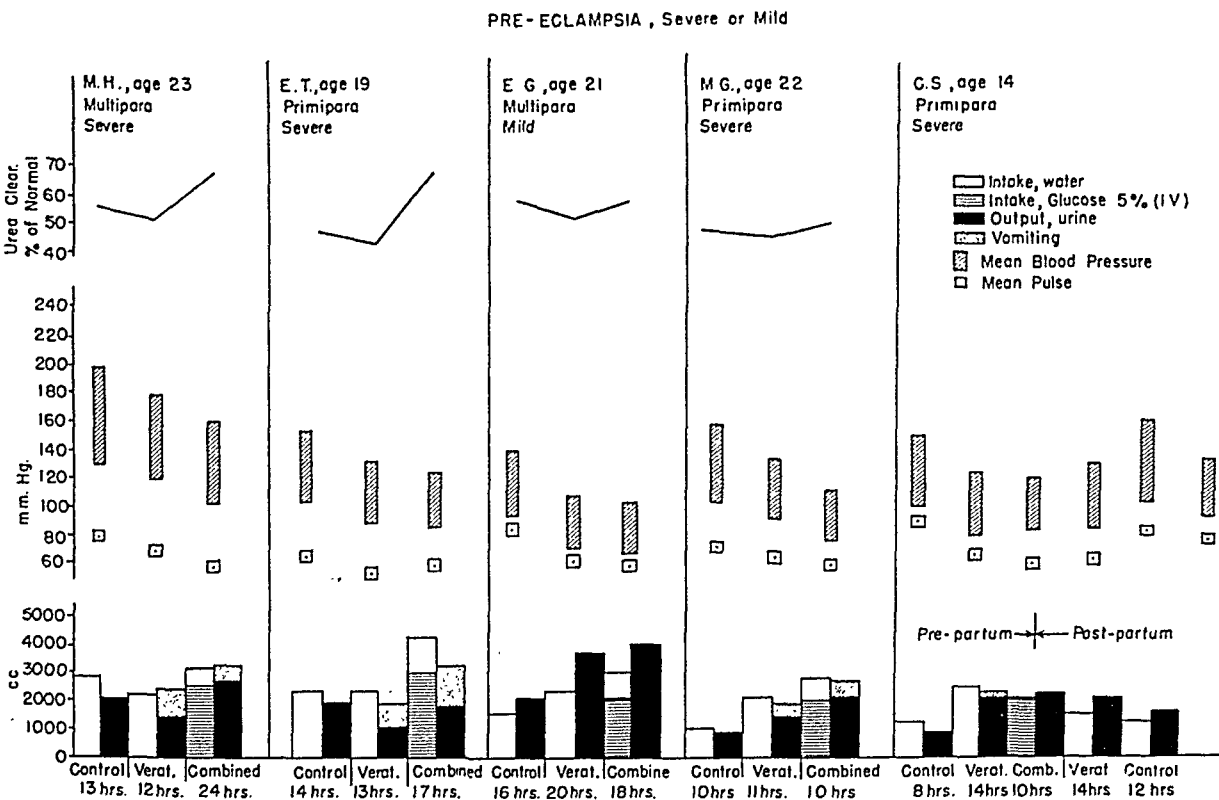


Fig. 4.—Total intake and output, mean blood pressure and pulse rate, and urea clearance variations in five pre-eclamptic patients during control, veratrum viride, and combined periods.

2. *Urea clearance*: This test was performed on six pre-eclamptic and two hypertensive patients. It showed some decrease following the veratrum viride administration but it returned to the original level or even higher during the combined period (Figs. 3, 4, 5). These oscillations in the urea clearance were considered within the range of variability usually attributed to this laboratory procedure.<sup>12</sup>

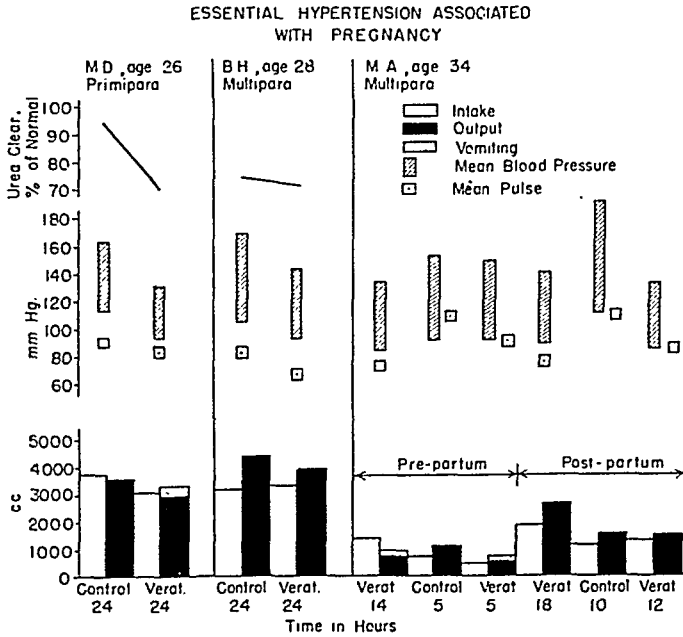


Fig. 5.—Total intake and output, mean blood pressure and pulse rate and urea clearance of the three hypertensive patients.

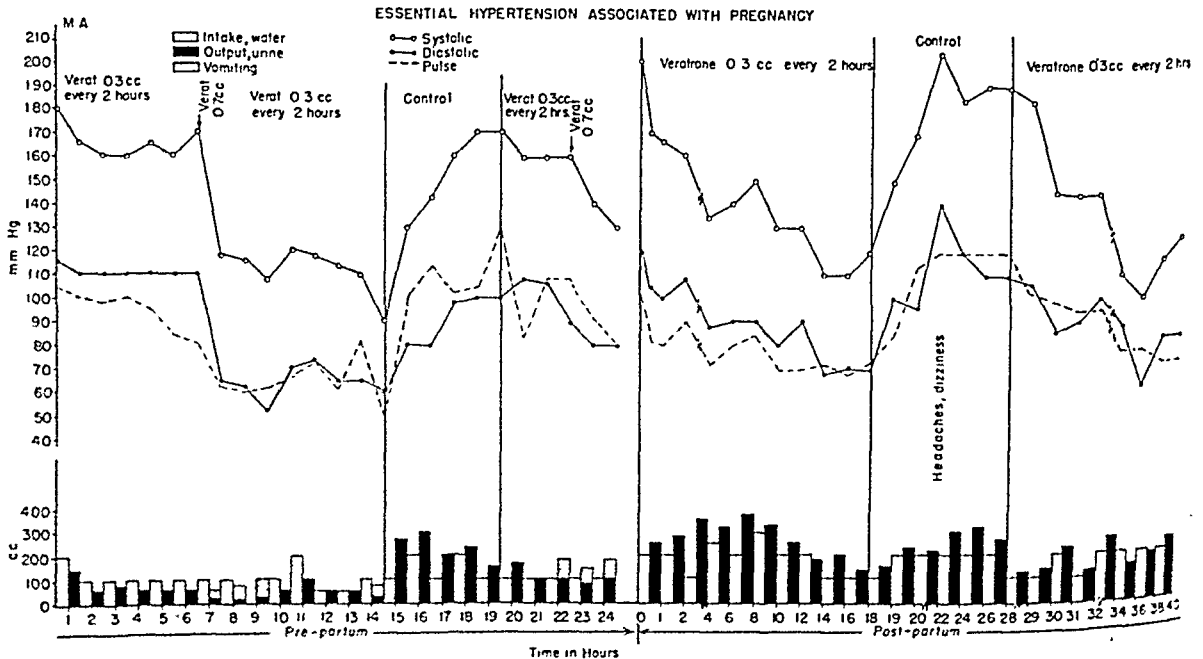


Fig. 6.—Alternating periods of control and veratrum viride administration in a patient with essential hypertension.

3. *Blood pressure and pulse rate:* In both pre-eclamptic and hypertensive groups the blood pressure and pulse rate were markedly decreased following the use of veratrum viride and paralleled each other. The greatest fall was 90 mm. Hg in the systolic and 60 mm. in the diastolic blood pressure. The lowest pulse rate recorded was 48.

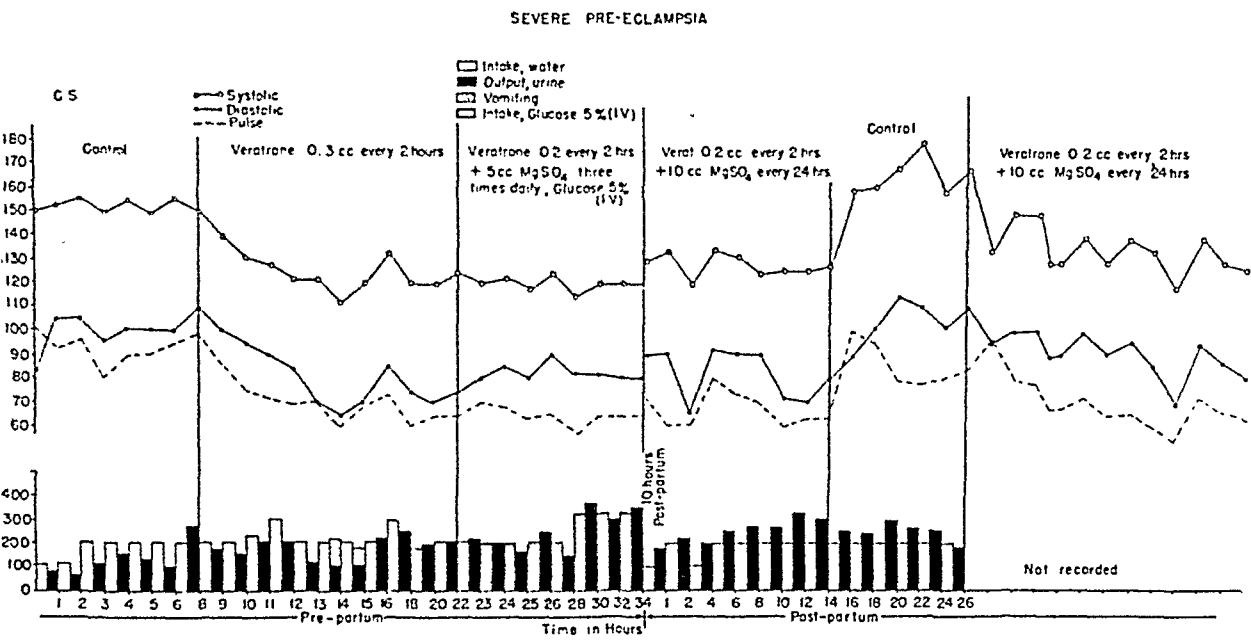


Fig. 7.—Alternating periods of control and veratrum viride administration in severe pre-eclamptic patient. Output in the last period was not recorded because the patient developed urethritis.

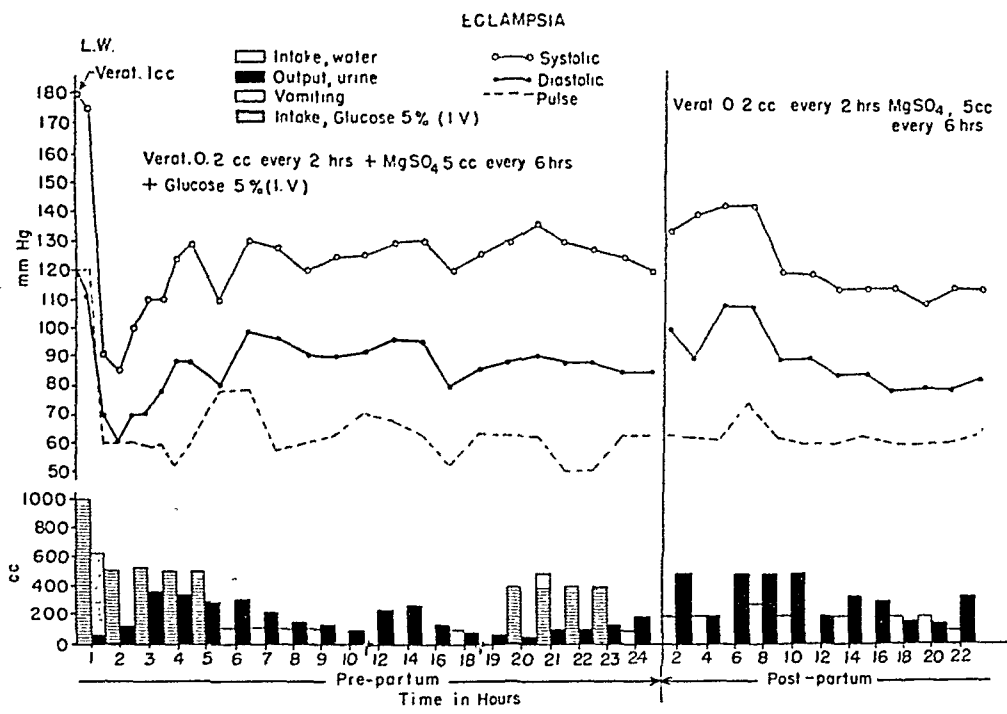


Fig. 8.—Pre- and postpartum study of an eclamptic patient who had no control period because of her poor condition.



ECLAMPSIA & CHRONIC KIDNEY DISEASE

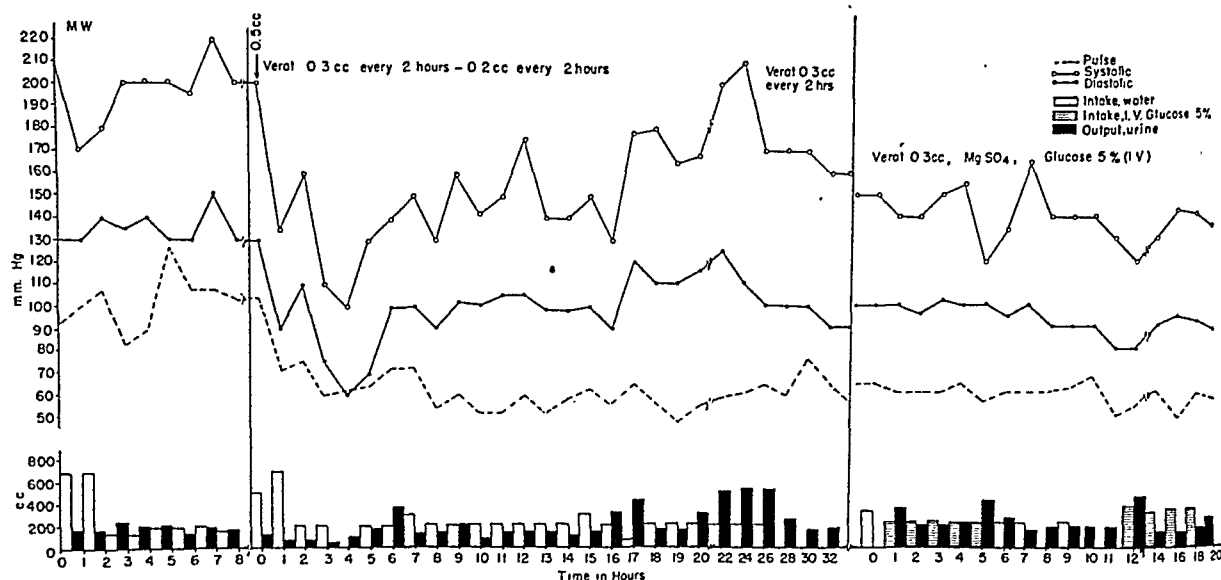


Fig. 9.—Blood pressure, pulse rate, and fluid balance of an eclampsia superimposed on chronic renal insufficiency. This patient left the hospital with blood urea nitrogen 60 and urine specific gravity 1.008.

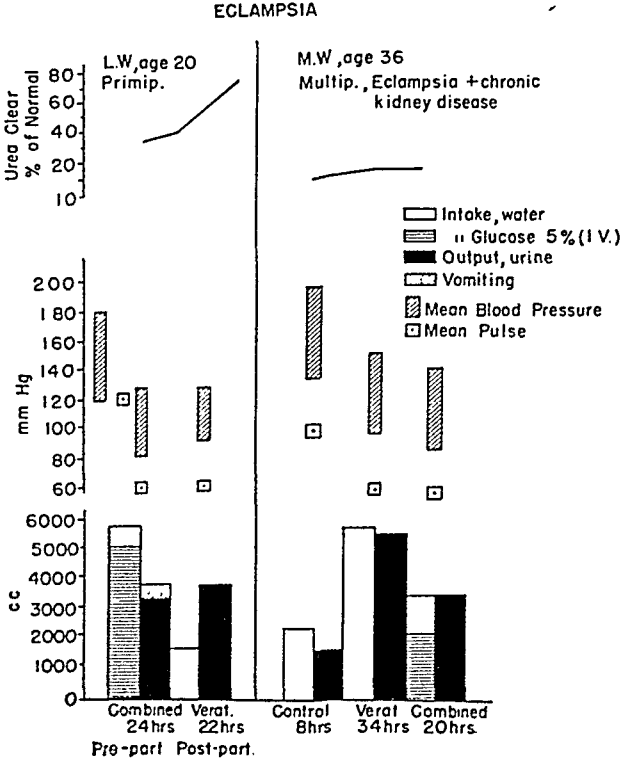


Fig. 10.—Total fluid balance, mean blood pressure, pulse rate and urea clearance variations of the two eclamptic patients.

In general, the patients with essential hypertension appeared to be more resistant to the action of veratrum viride, requiring larger doses to produce a satisfactory blood pressure fall.

C. *Eclampsia*.—Two patients with convulsive eclampsia were studied. The first (Fig. 8) was not studied in a control period due to the seriousness of her condition at the time of admission. She had had four convulsions at home and one upon arrival in the hospital. She was given 1 c.c. of veratrum viride within the first fifteen minutes and was continued then on the combined treatment before and after delivery.

1. *Urinary output*: The patient was catheterized at the time of admission, before the treatment was started, and no urine was obtained. After the next hour, the urinary output increased gradually and was maintained at an adequate volume, despite the marked fall in blood pressure and pulse rate. This patient showed profuse diuresis during the postpartum period.

2. *Urea clearance*: This test increased from 36.1 per cent to 42.2 per cent of normal while this patient was on the combined regimen before delivery, and to 76 per cent during the postpartum period.

The other eclamptic patient, who later proved to have chronic renal insufficiency, was studied for eight hours in the control period, thirty-six hours in the veratrum viride period and twenty-four hours in the combined period. Fig. 9 shows the urinary output and blood pressure variation in this patient. Fig. 10 illustrates the summary of both cases.

### Discussion

Little, as yet, is known about the pharmacological action of veratrum viride. Several investigators<sup>13, 14</sup> have made an extensive study of some of the veratrum alkaloids in animals and have concluded that they have a definite vasodepressor and cardiodecelerator effect acting partially through a vagal reflex. In their studies, there was no mention about the effect of these alkaloids on renal blood flow or urine volume. Willson and Smith,<sup>15</sup> however, by the use of intravenous injections of veratrum viride in vagotomized animals observed an increase in the perfusion rate of kidneys and other isolated organs. They maintained that this drug has a definite peripheral vasodilating action independent of the vagus nerve. It decreases the blood pressure and increases the vascular bed of isolated organs without demonstrable change in the cardiac output.

This peripheral vasodilatation, together with the increased blood flow, has served as the theoretical basis for the clinical use of veratrum viride in the toxemias of pregnancy.<sup>1-3</sup> However, when the drug was given to pre-eclamptic and hypertensive pregnant patients, Willson<sup>7, 8</sup> observed a simultaneous decrease in the urinary output which reached dangerous levels. This finding was explained on the basis of a sudden decrease in the blood pressure and blood volume, and increase in the circulation time.

Freis et al.<sup>16</sup> using the catheterization method (Fick), found no alteration in either cardiac output or renal blood flow in hypertensive nonpregnant patients treated with veratrum viride although they observed a transitory oliguria following the first few doses.

The analysis of our results revealed the presence of a definite but transitory decrease in the urinary output following the first dose of veratrum viride. In no instance, however, did this decrease reach dangerous levels of oliguria or anuria. Harmful effects or symptoms of shock were not observed in any patient, despite the marked fall in blood pressure and pulse rate. A compensatory polyuria occurred invariably despite the continuation of the treatment. Some



Robert Tilden Frank

1875—1949

## Pituitary Radiation for Sterility

To the Editor:

An evaluation of the results obtained in a comparatively large number of cases of sterility by the administration of estrogens and by pituitary irradiation is aptly presented in the September issue of the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY* by Dr. Rita Finkler. An impressive array of favorable reports by a number of investigators who employed the application of roentgen rays to the pituitary gland for this purpose is quoted, with emphasis on the therapeutic value of this procedure. It is obvious that the origin of this addition to the therapeutic armamentarium carries considerable interest. Credit for the introduction is given to Bécélère, who "in 1926 reported the beneficial results of roentgen irradiation of the pituitary in a case of secondary amenorrhea."

Based on extensive experimentation, which revealed the reciprocal interrelations between the anterior hypophysis and the ovaries and stressed the relative immunity of the adult brain to x-rays, a series of cases of functional bleeding and of bleeding due to fibroids were subjected to pituitary irradiation. The remarkable therapeutic results obtained were reported in 1922 (*Archiv für Gynäkologie*, vol. 117). Subsequently, the indications were amplified. In 1923 our report covered the experiences with this method in a considerable number of cases of functional bleeding, uterine fibroids, cervical carcinoma as a preliminary to radium insertion, diffuse hyperplasia of the thyroid, and ovarian insufficiency (*Archiv für Gynäkologie*, vol. 120). Menopausal symptoms and sterility were later additions to the list of indications. The rationale of pituitary irradiation in cervical carcinoma as an effective means of inhibition of abnormal hypophyseal activity was fully discussed in a thesis published in the *Journal of Obstetrics and Gynaecology of the British Empire*, vol. 46, 1939. Thus, radiation of the hypophysis in cervical and mammary carcinoma tended to ascertain the same principle which in the present underlies the utilization of testosterone for these purposes. It is gratifying to find in the modern literature various reports which corroborate our findings of "pseudomalignant changes in the endocervix of the pregnant uterus," as first described in this *JOURNAL*, June, 1933, and clearly demonstrate that the endocervix represents the target organ of the adenohypophysis and, in turn, of the ovary. The possibility that irradiation of the pituitary in sterility may have a specific influence on the secretion of the endocervix must be borne in mind.

J. HOFBAUER, M.D.

GIBSON HOTEL  
CINCINNATI, OHIO  
OCTOBER 1, 1949

## Reply by Dr. Finkler

To the Editor:

I have just received a letter from Dr. J. Hofbauer relative to my article entitled, "Evaluation of Hormonal and Radiation Therapy in 190 Cases of Functional Sterility and Secondary Amenorrhea" which appeared in the September, 1949, issue of the *JOURNAL*.

Unfortunately, I overlooked the matter of Dr. Hofbauer's priority in using radiation therapy to the pituitary gland and I will greatly appreciate it if you will be good enough to make this correction.

RITA S. FINKLER, M.D.

35 LESLIE STREET  
NEWARK, N. J.  
OCTOBER 4, 1949

# Items

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## American Board of Obstetrics and Gynecology

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Friday, Feb. 3, 1950.

Arrangements will be made so far as is possible for candidates to take the Part I examination (written paper and submission of case records) at places convenient for them. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination to be held May 21 to 28, inclusive, 1950, at the Shelburne, Atlantic City, N. J. Notice of the exact time and place of the Part I and Part II examinations will be sent all candidates well in advance of the examination date.

New Bulletins are now available for distribution upon application and give details of all changes in Board requirements and regulations made at the annual meeting of the Board held in Chicago, Ill., May 8 to 14, inclusive, 1949.

Application forms and Bulletins are sent upon request made to

PAUL TITUS, M.D., SECRETARY-TREASURER,  
AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY,  
1015 HIGHLAND BUILDING,  
PITTSBURGH 6, PA.

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## Increase in Size of the Journal

Our readers are notified that, beginning with the January issue, the JOURNAL will be enlarged to a total of 232 pages of reading matter. See announcement on page 36 of the advertising section of this number.

## Necrology

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DR. ROBERT TILDEN FRANK, gynecologist, eminent endocrinologist, a member of the Publication Committee, of the Advisory Editorial Board of the JOURNAL since its founding, and likewise the Editor of the Department of Book Reviews, died in New York City on October fifteenth after a brief illness, at the age of 74.

A native of New York, Dr. Frank received his A.B. at Harvard in 1905 and his M.D. at the College of Physicians and Surgeons in 1909. In 1906 he began his long association with the Mount Sinai Hospital, became attending gynecologist in 1925, and continued in this capacity until he was made consultant in 1937. He likewise founded the Endocrine Research Laboratory at the institution in 1925 and remained as its head until 1944. He did pioneer work in this field and was the first to demonstrate the female sex hormone in the follicular fluid of the human ovary.

During the first world war Dr. Frank served in France with the A.E.F. as a captain and on his return to this country found it necessary, for reasons of health, to reside in Colorado, where he became associated with the University and General Hospitals as attending gynecologist and also continued his studies in endocrinology. He was the author of many outstanding contributions to the literature in this field.

Dr. Frank was a member of many specialist societies, including the American Gynecological and the New York Obstetrical, which he had served as President.

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The Editor of the JOURNAL desires to add a personal note to the foregoing, for Robert Frank was closely associated with the early development of our publication and contributed much by his valuable advice and conscientious devotion to the work of his Department. The latter will be continued by Dr. Philip F. Williams of Philadelphia who was long associated with Dr. Frank in this capacity. The JOURNAL owes a tribute to the memory of Dr. Frank for his many years of active and helpful participation in its conduct.

### Materials and Methods

The following currently used commercial radiopaque media were used\*: Rayopake, Skiodan, Lipoidol, Iodochlorol, and Lipoiodine. The patients studied were selected from the Gynecologic Service of the University Hospital.

Altogether 200 women were subjected to hysterosalpingography. Absorption studies were conducted on 118 of these patients and are reported here. Thirty-eight of these patients subsequently were subjected to laparotomy for gynecologic disorders, and their pelvic tissues were studied for gross and microscopic evidence of inflammatory reaction. These results are being reported separately.

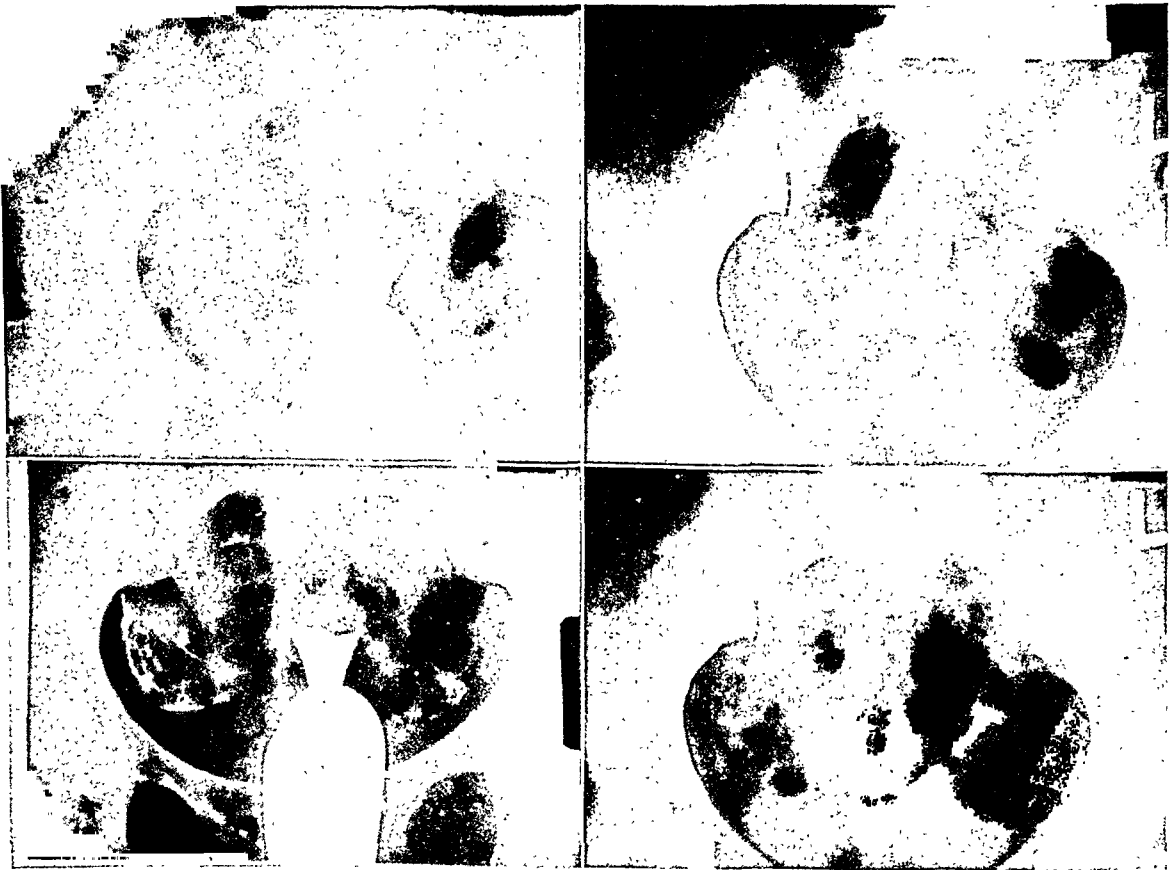


Fig. 1 (Case A. B.).—Absorption of Rayopake.

Upper left, Demonstrates tubal filling.

Lower left, Demonstrates peritoneal spill.

Upper right, Complete absorption (45 minutes).

Lower right, Bladder shadow (60 minutes).

The fractional method of injection without manometric control was employed. A total of 8 to 12 c.c. of medium was generally injected. Most of the patients experienced some pelvic discomfort during the procedure. In some, severe cramping pains like menstrual cramps were noted when the uterine cavity was overdistended by too rapid injection. This was relieved by withdrawing a small amount of the medium. Most patients experienced mild discomfort when the medium flowed into the peritoneal cavity. This varied in intensity with the individual patient but generally disappeared within an hour. In each case an attempt was made to demonstrate tubal filling

\*See Tables I and II for manufacturer.

# American Journal of Obstetrics and Gynecology

VOL. 58

DECEMBER, 1949

No. 6

## South Atlantic Association of Obstetricians and Gynecologists

*Transactions of the Eleventh Annual Meeting,  
February 10 to 12, 1949, at Williamsburg, Virginia*

### THE ABSORPTION OF RADIOPAQUE SUBSTANCES USED IN HYSTEOSALPINGOGRAPHY\*†‡

#### A Comparative Study of Various Aqueous and Oily Media

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J. T. BRADBURY, Sc.D., IOWA CITY, IOWA

*(From the Department of Obstetrics and Gynecology, University of Iowa College of Medicine)*

THERE are many reports in the literature on the persistence of various radiopaque substances in the pelvis for extended periods following hysterosalpingography, and several have contained unfavorable comments on certain media. Ries<sup>9</sup> and Lash<sup>5</sup> have stressed the foreign-body effects and resultant encysted masses produced by Lipiodol. Rubin<sup>11</sup> has corroborated these findings. Signs of peritoneal irritation and serious pelvic complications have been recorded by Flew,<sup>3</sup> Rubin,<sup>12</sup> Brun and Cortesi,<sup>2</sup> Lecerne and B  cl  re,<sup>6</sup> and Sicard and Solal.<sup>14</sup> The escape of Lipiodol into the utero-ovarian venous system with resultant pulmonary emboli has been reported by Zacharin,<sup>17</sup> Walther,<sup>16</sup> Lin and Tsou,<sup>7</sup> Roblee and Moore,<sup>10</sup> and Ingersoll and Robbins.<sup>4</sup>

Newer substances<sup>1, 8, 13, 15</sup> evolved in the last decade are said to overcome the objections to the slowly absorbed oil media by virtue of their physical properties and rapid absorption.

A study of the clinical suitability and absorbability of five radiopaque media was made to obtain information which might assist in selecting the most desirable agent. The present paper reports data obtained in the study of 118 cases.

\*Read at the annual meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Va., Feb. 10 to 12, 1949.

†The Foundation Prize Award Thesis.

‡This study was made possible by a grant from the Hoffmann-La Roche Company.

NOTE: The Editors accept no responsibility for views and statements of authors as published in their "Original Communications."



of these were found to have hydrosalpinx at operation with complete occlusion of the fimbriated ends of the tubes. Bladder shadows were demonstrated within one hour in the majority, indicating the rapidity of renal excretion of this medium.

TABLE I. ABSORPTION OF AQUEOUS RADIOPAQUE MEDIA

MEDIUM	TOTAL NO. CASES	ABSORPTION TIME							
		LESS THAN 25 MINUTES		25-45 MIN.		45-75 MIN.		2-5 HOURS*	
		NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Rayopake (Hoffmann-La Roche)	52	7	13	37	71	4	8	4	8
Skiodan (Winthrop)	24	3	13	16	67	1	4	4	16

The subjects were injected with 6 to 12 c.c. of the agent and studied by serial films at ten-minute intervals.

\*Delayed absorption occurred in eight cases of hydrosalpinx. This is of diagnostic value in determining tubal occlusion.

TABLE II. OILY RADIOPAQUE MEDIA

MEDIUM	TOTAL NO. CASES	PERSISTENCE OF RADIOGRAPHIC SHADOWS*							
		1-3 MONTHS*		3-6 MONTHS*		7-14 MONTHS*		OIL RETENTION CYSTS†	
		NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Lipiodol (Fougera)	16	7	44	5	31	4	25	4	25
Iodochlorol (Searle)	17	11	68	8	32	0		4	25
Lipiodiodine (Ciba)	10	5	50	5	50	0		1	10

These subjects were injected with oily radiopaque agents and followed by serial films at monthly intervals. Radiopaque shadows were present when these patients were seen for the last time.

\*This represents the length of time these patients were followed; radiopaque pelvic shadows were present when last filmed.

†Thick-walled cystic dilatations of the tubal lumina filled with inspissated oil and bound down in the pelvis by adhesions. Microscopically they show foreign-body reaction, calcification and fibrosis of the tube wall. On x-ray they appear as large isolated pelvic shadows which are quite constant from month to month. They may connect with similar adjacent cystic structures in the pelvis.

*Lipiodol* is very slowly absorbed from the pelvis. In the sixteen women injected with *Lipiodol*, x-ray shadows indicating unabsorbed oil deposits persisted throughout the period of observation up to fourteen months; 44 per cent in one to three months; 31 per cent in three to six months; and 25 per cent of the subjects in seven to fourteen months (Table II and Fig. 3). Four of these patients showed fairly large discrete pelvic x-ray shadows which were constant month after month. Two of these women were later subjected to operation and these structures were found to be "oil-retention cysts" (Figs. 3 and 9).

*Iodochlorol* is also slowly absorbed from the pelvis (Table II and Fig. 4). In sixteen women injected with this medium, the oil shadows were still present one to six months later. Persistent oil shadows were observed in all patients when last seen. Four patients showed persistent x-ray shadows which were constant for six months.

*Lipiodiodine* is also slowly absorbed from the pelvis (Table II and Fig. 5). In ten subjects studied, the absorption time varied from one to six months; fifty per cent of the cases showed persistent oil shadows when last seen at three to six months. One patient presented pelvic x-ray shadows of an oil cyst. It is apparent from a comparison of Figs. 3, 4, and 5 that *Lipiodiodine* is better absorbed than the other oily media. While this series is small (ten subjects) it is our clinical impression that this difference in absorption is significant, and that *Lipiodiodine* is the most rapidly absorbed of the oily agents.

and peritoneal spill, and to follow absorption from the peritoneal cavity by a succession of films. Four to six serial films were usually obtained. When aqueous media were used the absorption time was followed by films taken at ten-minute intervals. Patients injected with oily media were filmed at monthly intervals.

### Clinical Data

#### Absorption.—

*Rayopake* is very rapidly absorbed from the peritoneal cavity and upper genital tract. In 90 per cent of the 52 cases, absorption was complete in 75 minutes; 13 per cent in less than 25 minutes; 71 per cent in between 25 and 45 minutes, and 8 per cent in 45 to 75 minutes (Table I and Fig. 1). In four women (8 per cent), large smooth pelvic x-ray shadows were still present after two to five hours, and at later operation all showed evidence of hydrosalpinx with complete occlusion of the fimbriated tubal ends (Fig. 6). In the majority of the patients, a distinct bladder shadow appeared within one hour, indicating the rapidity of renal excretion of the substance.

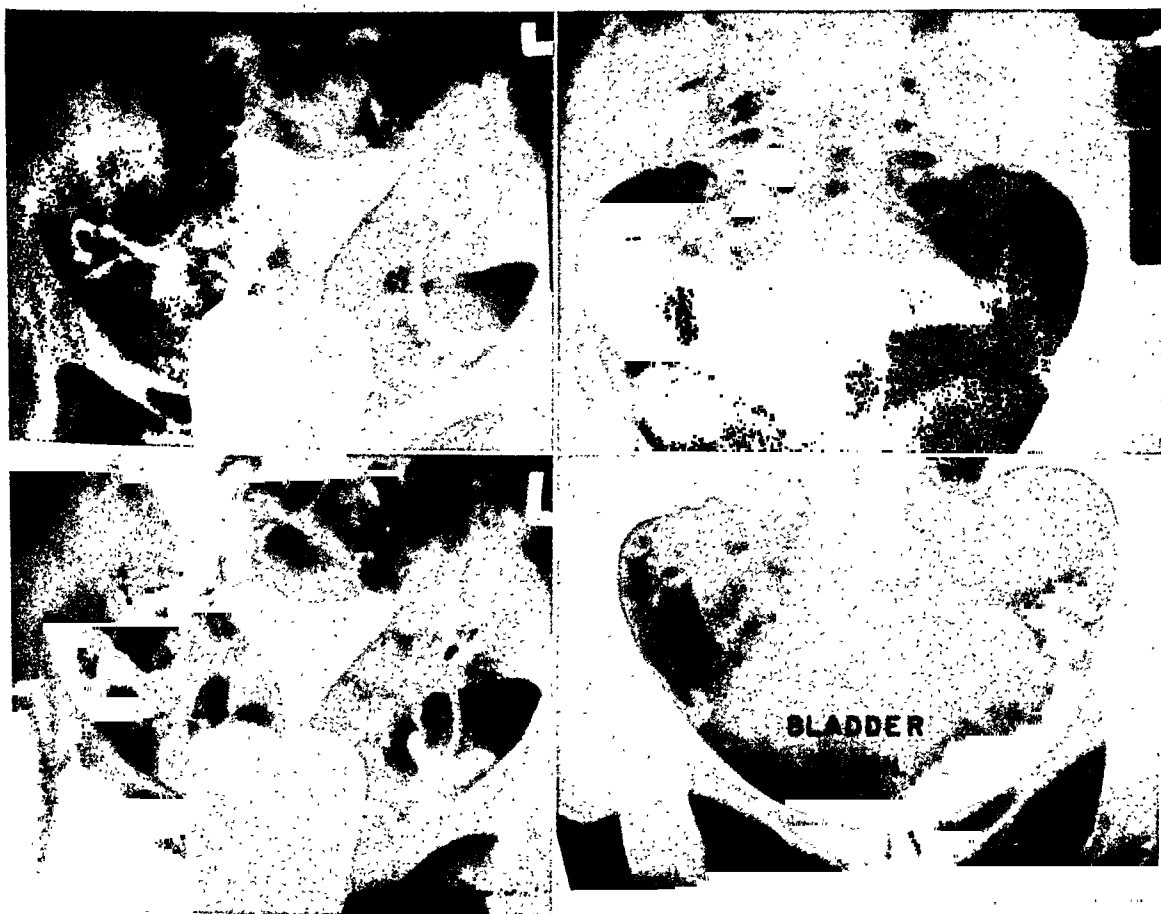


Fig. 2 (Case E. T.).—Absorption of Skiodan acacia.

Upper left, Demonstrates tubal filling.

Lower left, Demonstrates peritoneal spill.

Upper right, Almost complete absorption (25 minutes).

Lower right, Demonstrates bladder shadow (50 minutes).

*Skiodan acacia* is likewise rapidly absorbed from the pelvis (Table I and Fig. 2). In 84 per cent of the 24 cases, absorption was complete within 75 minutes; 13 per cent in less than 25 minutes; 67 per cent between 25 and 45 minutes; and 4 per cent in 45 to 75 minutes. Four women (16 per cent) showed large smooth x-ray shadows after two to five hours (similar to Fig. 6). Three

*Iodochlorol*: Excellent tubal visualization was obtained in the sixteen patients injected with Iodochlorol. There was gradual emptying of the tubes in each case. Successive films demonstrated tubal outline and pelvic spill very satisfactorily. The radiographic shadows were excellent and the details were sharp and distinct (Fig. 4).



Fig. 4 (Case M. H.).—Absorption of Iodochlorol.  
Upper left, Demonstrates tubal filling.  
Lower left, Demonstrates peritoneal spill.  
Upper right, Persistence of iodized oil (53 days).  
Lower right, Persistence of iodized oil (119 days).

*Lipiodine*: Ten subjects were injected with Lipiodine. The low viscosity of this medium permitted too rapid peritoneal spill, which overshadowed the tubal outline and made satisfactory films of tubal detail difficult to obtain. The density of the x-ray shadows was excellent (Fig. 5).

#### *Clinical Reactions.*—

*Rayopake*: One patient (2 per cent) with radiographic evidence of tubal disease developed lower abdominal pain, fever (101° F.), and leucocytosis three days following Rayopake injection. Response to treatment with antibiotics was prompt. Another patient with a history of allergy and drug sensitivity developed generalized urticaria following injection.

*Skiodan*: Three patients (13 per cent) injected with Skiodan acacia solution developed generalized hives with severe itching; there was no history of allergy or drug sensitivity. They responded to treatment with subcutaneous Adrenalin.

*Viscosity and Radiopacity.—*

*Rayopake:* In the 52 patients injected with Rayopake, complete tubal visualization was usually obtained following the first or second serial injection. Subsequent injections demonstrated peritoneal spill and gradual emptying of the tubes. The density of the radiographic shadows was satisfactory in all cases, the details being sharp and distinct (Fig. 1).



Fig. 3 (Case E. F.).—Absorption of Lipiodol.  
Upper left, Demonstrates tubal filling.  
Lower left, Demonstrates peritoneal spill.  
Upper right, Persistence of iodized oil (74 days).  
Lower right, Persistence of iodized oil (179 days).

*Skiodan:* In the 24 patients injected with Skiodan acacia solution, there was such rapid emptying of the tubes after the first or second serial injection that in many instances the peritoneal spill overshadowed the tubal outlines (Fig. 2). For this reason films showing tubal detail were difficult to obtain and not satisfactory. The density of the x-ray shadows, while lightest of the group studied, was satisfactory. The least agitation of this medium produced bubbles which gave false shadows in many films (Fig. 7).

*Lipiodol:* In sixteen women injected with Lipiodol, there was a more gradual tubal filling permitting excellent tubal visualization. Successive films demonstrated pelvic spill very satisfactorily. The radiographic shadows were excellent, the details being sharp and distinct (Fig. 3).

pre-eclamptic patients (Fig. 11 as an example), because of delayed excretion of fluid intake, showed periods of transitory oliguria and compensatory polyuria even when they were not under any treatment. This might have led to incorrect conclusions had these patients not been observed for a long period of time.

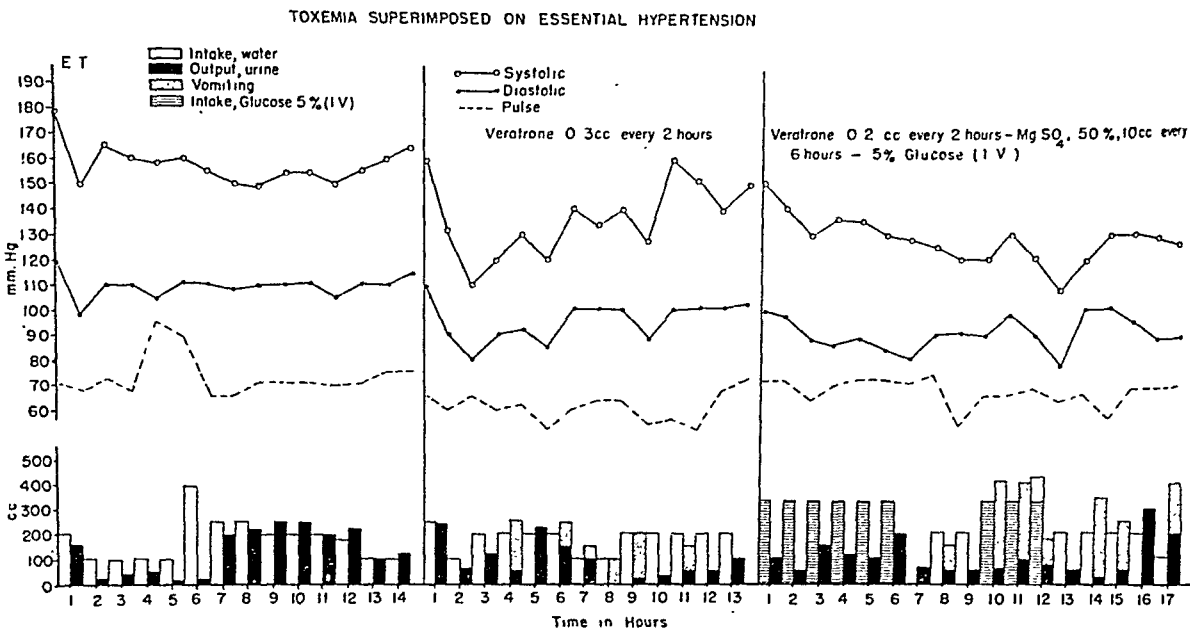


Fig. 11.—Severe pre-eclampsia with underlying essential hypertension. Note the two-hour oliguria in the control period. This patient tolerated veratrum viride poorly. Severe vomiting occurred even with small doses.

Further scrutiny of these data indicated that the decrease in urine volume was more marked when the following conditions existed:

- A sudden fall in blood pressure and pulse rate consequent to the use of a large dose of the drug,
- Severe vomiting and profuse diaphoresis leading to a loss of a large quantity of fluid by routes other than the kidneys,
- When the fluid intake (already impaired by the nausea, vomiting, and diaphoresis peculiar to the action of veratrum viride) was insufficient to replace the fluid loss.

That a correlation between the sudden drop in blood pressure and the decrease in urine volume exists was evidenced by the fact that when veratrum viride was employed in proper dosage, not allowing the former to fall below 120 to 140 systolic and 80 to 90 diastolic, adequate diuresis was obtained. It could also be corroborated by the fact that, in the cases of normal pregnancy, where no decrease in blood pressure was noted with veratrum viride, the urine volume, similarly, showed no change.

Nausea, vomiting, and diaphoresis were considered important factors in decreasing the urinary output. The figures indicate that the lowest urine volumes were coincident with severe vomiting. With the use of proper dosage of veratrum viride these disturbing elements were minimal and the patients increased their oral fluid intake and consequently their urinary output.

*Lipiodol*: One of the patients (8 per cent) injected with Lipiodol developed lower abdominal pain, fever ( $102^{\circ}$  F.), and leucocytosis four days following Lipiodol injection. There was no radiographic evidence of tubal disease. Two sterility patients showing isolated pelvic x-ray shadows five and fourteen months subsequent to Lipiodol injection came to operation. These shadows were found to represent occluded tubes in which the iodized oil was entrapped (Fig. 8). These cysts were bound down by adhesions, contained inspissated oil, and the walls showed considerable foreign-body reaction microscopically (Fig. 9). Three other women who had hysterectomies a few days following the Lipiodol injections had from  $1\frac{1}{2}$  to 2 ounces of free, brown, serous fluid in the pelvis.



Fig. 5 (Case B. E.).—Absorption of Lipoiodine.  
Upper left, Demonstrates tubal filling.  
Lower left, Demonstrates peritoneal spill.  
Upper right, Persistence of iodized oil (21 days).  
Lower right, Persistence of iodized oil (84 days) (almost complete absorption).

*Iodochlorol*: There were no clinical reactions noted in this group of subjects. At the time of laparotomy following Iodochlorol injection, there were from  $1\frac{1}{2}$  to 2 ounces of free, brown, serous fluid in the pelvis.

*Lipoiodine*: Two cases of severe septic reaction followed the use of Lipoiodine. Although the Lipoiodine series is small and the role of the iodized oil is in doubt, it is of interest that the only woman in this entire series in whom severe septic complications occurred had been injected with Lipoiodine.

#### *Histologic Reactions.*—

Tissue reaction to these various media was studied both grossly and microscopically. These observations are being reported separately but may be summarized as follows:

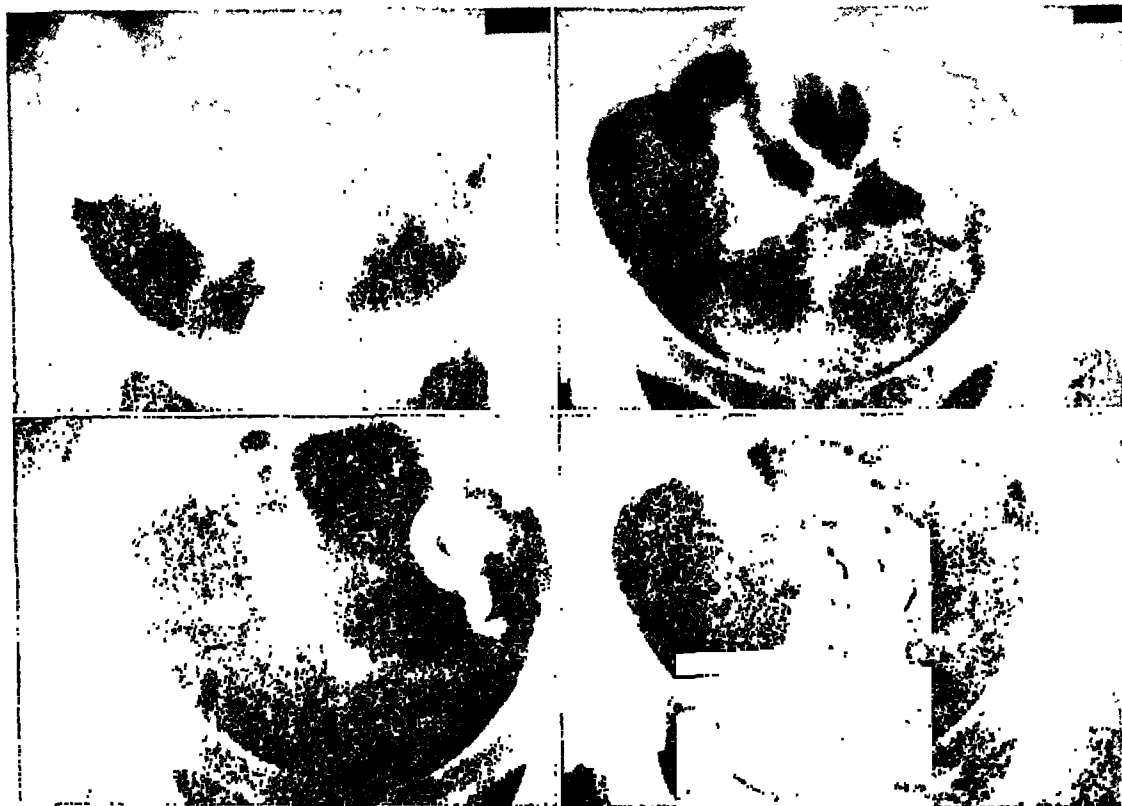


Fig. 6 (Case J. E. C.).—Delayed tubal absorption of Rayopake (hydrosalpinx).

Upper left, Demonstrates tubal filling.

Lower left, Demonstrates tubal shadows at end of one hour.

Upper right, Demonstrates tubal shadows at end of three hours.

Lower right, Demonstrates complete absorption at end of five hours.



Fig. 7.—Skiodan acacia films showing false intrauterine shadows produced by bubbles.

Right, Many small bubbles.

Left, Large bubble.



Fig. 8 (Case H. L.).—Lipiodol oil-retention cyst.  
Left, Hysterosalpingogram, Sept. 12, 1946.  
Right, Left oil-retention cyst, Feb. 12, 1947. (See Fig. 9.)

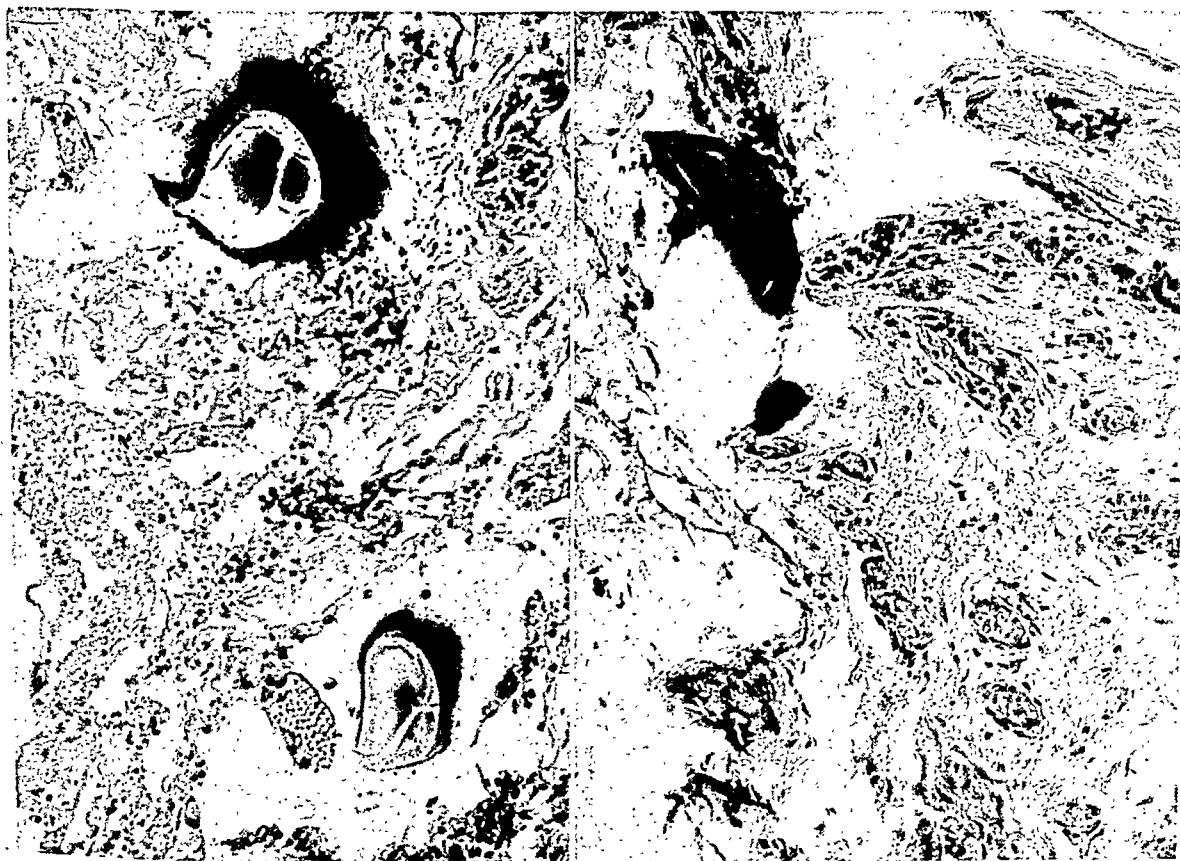


Fig. 9.—Microscopic sections of oil-retention cysts.  
Left, Calcification of Lipiodol. Oil-retention cyst found in H. L. (Fig. 8).  
Right, Oil-retention cyst showing foreign body giant cells and psammoma body.  
Iodochlorol, Case G. W.



In normal tubes no significant reaction to either the aqueous media or iodized oils occurs. However, in the presence of partial or complete tubal obstruction, the iodized oils produce foreign-body granulomas which bring about complete occlusion and "oil-retention cysts." Transient acute peritoneal reactions are found in patients injected with the iodized oils. These undesirable effects are not manifested by the aqueous media because of their rapid absorption and nonirritating effects.

### Discussion

Clinical results with all the radiopaque substances have been generally satisfactory. While certain individual differences exist, these media can be divided into the oily and aqueous agents and discussed as groups. These observations are tabulated in Table III.

TABLE III. TABULATION OF CLINICAL DATA

	AQUEOUS		OILY		
	RAYOPAQUE 52 CASES	SKIOPAN ACACIA 24 CASES	LIPIODOL 16 CASES	IODOCHLOROL 17 CASES	LIPOIODINE 10 CASES
Absorption time	Less than hour	Less than hour	6-9 plus months	6-9 plus months	3-6 months
Route of excretion	Kidney	Kidney	?	?	?
Viscosity	Satisfactory	Unsatisfactory	Requires warming; satisfactory	Requires warming; satisfactory	Solid at room temperature; unsatisfactory
Radiopacity	Good	Good	Excellent	Excellent	Excellent
Time of filming	Immediately	Immediately	Delayed	Delayed	Delayed
Clinical reaction allergic and septic (see text)	Rare, 4%	Allergic reaction in 13%	Occasional, 8%	None in this series	20%
Tissue reaction	None	None	Present	Present	Present
Retention cysts	None	None	Present	Present	None seen
Facility in handling	Satisfactory	Poor	Fair	Satisfactory	Fair

Rapidity of absorption constitutes one of the outstanding differences. The oily agents persist in the pelvis for months. The method of absorption and excretion has not been determined. The aqueous media on the other hand are absorbed within 20 to 40 minutes and are excreted through the kidney; a bladder shadow is usually visible within an hour (Fig. 1). In partially or completely occluded tubes the shadows tend to persist. With the oily media it is impossible to determine with certainty by radiography whether the shadow represents an oil pocket in the peritoneal cavity or trapped oil in an occluded tube. The aqueous media on the other hand show a characteristic delayed absorption pattern which is not present in peritoneal spill (Fig. 6).

This rapidity of absorption of the aqueous group requires certain modifications in radiographic technique. The patient must be on an x-ray table when injected and films taken at once. Physicians who are accustomed to injecting patients in their offices and sending them to the radiologist for films would object to the rapid absorption of the aqueous media. This apparent disadvantage is easily compensated for, and is more than offset by, the many disadvantages associated with the persistence of iodized oil in the pelvis.

The radiographic shadows of both types of agents are satisfactory. Although the aqueous media produce less dense shadows than the oily preparations, this presented no difficulties.

The viscosity of the radiopaque media also plays an important part in the accurate diagnosis of tubal disease. The medium must be sufficiently viscous to remain in the tubes long enough to permit satisfactory x-ray films. Most of the agents studied were satisfactory in this regard. The viscosity of Rayopake and Iodochlorol is satisfactory. Skiodan Acacia on the other hand is considerably less viscous, the material spilling into the peritoneal cavity so rapidly that the tubes are occasionally empty on filming, or the peritoneal spill overshadows the tubal outline.

Lipiodol and Lipoiodine require warming prior to use. This is especially true of Lipoiodine which is solid at room temperature. Heating to liquefaction so reduces the viscosity of the oil that unsatisfactory radiographic films similar to those described for Skiodan Acacia are often obtained. It is apparent from these studies that viscosity plays an important part in obtaining satisfactory radiographic shadows. Rayopake of the aqueous and Iodochlorol of the oily group were most satisfactory from this standpoint.

The physical properties of these agents are important from the standpoint of satisfactory handling. The necessity of heating Lipiodol and Lipoiodine is a distinct disadvantage. Skiodan Acacia solution is a sticky substance, frequently causing the plunger of the syringe to bind; it also occasionally forms bubbles on agitation and if accidentally introduced into the uterus or tubes may give false shadows.

Patients experience some discomfort with hysterosalpingography and it frequently is necessary to administer a narcotic. Pain associated with this procedure is of three types: the discomfort associated with attaching the tenaculum and introducing the cannula; the pain of uterine distention; and the pain associated with peritoneal spill. The amount of discomfort experienced by patients in each of these three categories varies widely. Some authors have tended to assign more or less pain to some one of the agents used. This study offered an opportunity to inject a number of patients with two or more media, thus providing an opportunity to compare the several substances in the same patient.

The discomfort of the tenaculum and cannula cannot be significantly altered. The pain associated with uterine distention can be minimized by slow injection of the medium and, if significant, can be relieved by the withdrawal of a small quantity. The discomfort associated with peritoneal spill varies little with the different agents used. The degree of pain seems to reflect the patient's sensitivity to the peritoneal spill of a foreign substance rather than to the chemical characteristic of the agent employed.

The observed clinical reactions predominate with two substances. Thirteen per cent of the patients injected with Skiodan Acacia developed hives. Lipoiodine was associated with severe pelvic infection in two patients; one developed an abscess requiring drainage and the other a chronic cellulitis requiring sev-

eral months for resolution. While this series is small it is of interest that two of the three febrile reactions and both the septic complications occurred with Lipoiodine.

Tissue reaction to these agents may be immediate or delayed. Both seem to be absent with the aqueous media. Oily substances produce a transient peritoneal reaction as manifested by brownish fluid and edema of the pelvic peritoneum in twenty-four and forty-eight hours, and filmy adhesions in a week. Persistent oil in the pelvis frequently produces oil-retention cysts, chronic granulomas, and psammoma bodies. The earliest time at which this reaction was found was seventy-one days; others ranged from twelve to fourteen months. Patients who apparently have partially occluded tubes may suffer complete closure as a result of this chronic inflammatory change in the tube induced by the persistence of iodized oil.

### Summary

1. Hysterosalpingograms were obtained on two hundred subjects in a study of aqueous and oily radiopaque media. The clinical problems encountered with these agents are outlined.

2. Absorption of radiopaque materials varied from 25 to 45 minutes with aqueous media to 3 to 6 months with the iodized oils.

3. Satisfactory radiographic visualization of the upper genital tract was obtained with Rayopake of the aqueous media and Lipiodol and Iodochlorol of the oily media.

4. Iodized oils have the following *advantages*:

- a. Dense radiographic shadows.
- b. Longer period (several hours or days after injection) during which x-ray films for tubal patency can be taken.

5. The oily media have the following *disadvantages*:

- a. Retention of oil for months.
- b. Transient acute peritoneal reaction.
- c. Development of oil retention cysts with foreign-body granulomas and psammoma bodies.
- d. Oil emboli (none observed in this study).

6. Aqueous radiopaque media have the following *advantages*:

- a. Rapid absorption.
- b. Rapid renal excretion.
- c. Satisfactory physical properties for handling.
- d. Elimination of the hazard of "oil-retention cysts" and pulmonary emboli.
- e. Satisfactory radiographic shadows.

7. The aqueous radiopaque media have certain limitations:

- a. Rapidity of absorption, requiring that films be taken within 5 to 10 minutes after injection.
- b. Low viscosity of Skiodan Acacia permitting too rapid peritoneal spill, overshadowing the tubal outlines.

## Conclusions

The aqueous radiopaque agents are preferable in hysterosalpingography because of their rapid absorption and relative freedom from the many untoward reactions encountered with the oily media.

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Rouques, L.: *A Practical Method to Encourage Suckling in Premature Infants*, Presse méd. 56: 433, June 19, 1948.

The author reviews Laura Landucci's article entitled "The sympathomimetic amines in the treatment of the premature infants" which appears in *Il Lattante* 18: 598-602, 1947. She cites Gaal and Katona's study wherein they used the hydrophosphate of alpha-phenyl-Beta-isopropylamine upon 71 cases. They concluded that a dosage of 2.0 mg. administered three times daily provided an efficient means of increasing the amount of breast milk taken by prematures.

Landucci used another derivative of benzedrine, namely Beta-phenyl-isopropylamine upon fourteen prematures—the average weight was around 1,400 Gm. In all cases the quantity of milk consumed by each was rapidly increased with the prematures responding as actively as infants at term to suckling. They cried before feeding and slept soon after. None showed signs of drug intolerance.

She uses 1.0 mg. in a morning dose which if insufficient is gradually increased, little by little, up to 4.0 mg. in two doses. The drug is not used at night so the premature can sleep without stimulation. In general, after eight to twelve days, the prematures were sufficiently developed that the drug could be dropped at the end of these times.

CLAIR E. FOLSOME.

Deroberst, L.: *Bronchial Obstruction of the Newborn. Intrauterine Suffocation*, Presse méd. 56: 444-445, June 23, 1948.

The author illustrates, with the aid of six illustrations, three black and white microphotographs and three colored drawings, that bronchial obstruction, caused not only by amniotic fluid but also by plugs of vernix caseosa, albumin, mucus, or blood clots, produces severe asphyxia phenomena. These observations justify more serious attempts at removal of such bronchial obstructions. The illustrations are excellent.

CLAIR E. FOLSOME.

# A FOLLOW-UP STUDY OF TWO HUNDRED FORTY-THREE CASES OF ECLAMPSIA FOR AN AVERAGE OF TWELVE YEARS\*

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THE primary purpose of this study is to throw some additional light on the much discussed question of whether or not eclampsia leaves irreparable vascular and renal damage and is a causative factor in subsequent hypertensive cardiovascular disease.

Two hundred forty-three cases of eclampsia in 138 white patients and 105 Negroes, occurring at the University Hospital, Augusta, Ga., from 1919 to 1947, were followed and the patients were seen and studied at least once from one to twenty-eight years later, the average length of time being 12.3 years—13.9 years for the white patients and 8.2 years for the Negroes.

Most of these women were interviewed and examined during the period from Jan. 1, 1948, through Aug. 31, 1948. In some cases when the patients themselves could not be found, the information was taken from hospital records of subsequent admissions, if such charts contained adequate information.

## Material

*Age.*—The mean age at the time of follow-up examination was 32.6 years. The Negro women were about 6 years younger than the white, 29.2 and 35.4 years, respectively.

*Subsequent Pregnancies.*—During this time there had been 565 subsequent pregnancies in 188 women. Seventy-seven and four-tenths per cent of the women had at least one additional pregnancy. Eighty-three and three-tenths per cent of the white women had 341 pregnancies and 69.5 per cent of the Negro women had 224 pregnancies. The smaller number of pregnancies among the Negroes is due in part, of course, to the shorter average period of time elapsed. It may also be due to the high incidence of gonorrheal salpingitis in these women.

*The Fetus.*—Of the 565 pregnancies, 436, or 77.2 per cent, resulted in live-born infants and 129, or 22.9 per cent, resulted in either stillbirths or abortions.

No attempt was made to differentiate between stillbirth and abortion because of the inability of many of these women to give an accurate history. Also, the figure given for the fetal mortality should probably be higher, because there are undoubtedly a certain number of abortions not recalled, some early ones not recognized, and perhaps some criminal abortions which were concealed. This, of course, would raise not only the incidence of fetal mortality, but the total number of pregnancies as well.

Taussig<sup>1</sup> has proved that no statistics on abortion are ever entirely accurate, and Greenhill<sup>2</sup> and Stander<sup>3</sup> also bring out this point. However, going on the assumption that one set of figures may contain approximately the same percentage of errors as another, we may make some comparison to the usual incidence

\*Read at the annual meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Va., Feb. 10 to 12, 1949.

of stillbirths and abortions. Stander<sup>3</sup> reports an incidence of stillbirths of 2.14 per cent, and from 8 to 10 per cent abortions. Greenhill<sup>2</sup> says that in the United States in 1944, 39.8 labors out of 1,000 did not result in a live infant. This is an incidence of 3.98 per cent stillbirths. It may be seen, therefore, that in these pregnancies there was a fetal mortality almost twice as great as would be expected. Dieckmann,<sup>4</sup> Rucker,<sup>5</sup> Sym,<sup>6</sup> and others have noted a similar increase. This is in line with the "toxemic sequence" of Young<sup>7, 8</sup> but not necessarily due to "some morbid influence" in their bodies as he concluded. This will be discussed later.

*Subsequent Toxemia.*—At least 203, or 36.1 per cent of all subsequent pregnancies, were complicated by toxemia. Of those women with subsequent pregnancies, 106, or 56.4 per cent, had at least one episode of toxemia. The figures are probably too low, due to the unreliability of the history, as mentioned in regard to abortion, but we may safely say that the incidence of toxemia was at least four to six times greater than would be expected in the general run of pregnancies.<sup>1, 3, 4, 24, 25</sup> Other authors<sup>4-23</sup> have also found an increase in the number of toxemias in post eclamptic and post toxemic pregnancies, and Page and Cox,<sup>14</sup> from collected statistics, state the the incidence is eight to ten times more than that usually found.

TABLE I. NUMBER OF PATIENTS INCLUDED IN THIS STUDY, MEAN PERIOD OF TIME COVERED, MEAN AGE AT LAST FOLLOW-UP EXAMINATION, AND NUMBER OF PREGNANCIES SUBSEQUENT TO THE ORIGINAL ATTACK OF ECLAMPSIA

	NUMBER OF PATIENTS	MEAN NUMBER OF YEARS FOLLOWED	MEAN AGE AT TIME OF FOLLOW-UP	NUMBER OF SUBSEQUENT PREGNANCIES	NUMBER OF WOMEN WHO HAD SUBSEQUENT PREGNANCIES	PER CENT OF WOMEN WHO HAD SUBSEQUENT PREGNANCIES
White	138	13.9	35.4	341	115	83.3
Negro	105	8.2	29.2	224	73	69.5
Total	243	12.3	32.6	565	188	77.4

TABLE II. FETAL MORTALITY OF SUBSEQUENT PREGNANCIES AND INCIDENCE OF SUBSEQUENT TOXEMIA

	PER CENT OF SUBSEQUENT PREGNANCIES WHICH RESULTED IN STILLBIRTH OR ABORTION	PER CENT OF SUBSEQUENT PREGNANCIES WHICH WERE TOXEMIC	PER CENT OF WOMEN WITH SUBSEQUENT PREGNANCIES WHO HAD SUBSEQUENT TOXEMIA	PER CENT OF SUBSEQUENT PREGNANCIES WHICH WERE ECLAMPTIC	PER CENT OF WOMEN WITH SUBSEQUENT PREGNANCIES WHO HAD SUBSEQUENT ECLAMPSIA
White	23.2	39.3	63.5	5.3	14.8
Negro	21.9	30.8	45.2	4.0	12.3
Total	22.9	36.1	56.4	4.8	13.8

TABLE III. INCIDENCE OF TOXEMIA IN PREGNANCIES OCCURRING PRIOR TO THE ORIGINAL ATTACK OF ECLAMPSIA IN THESE WOMEN

	NO. OF PREGNANCIES PREVIOUS TO THE ORIGINAL ATTACK OF ECLAMPSIA	NO. OF WOMEN WHO HAD PREVIOUS PREGNANCIES	PER CENT OF WOMEN WHO HAD PREVIOUS PREGNANCIES	PER CENT OF PREVIOUS PREGNANCIES WHICH WERE TOXEMIC	PER CENT OF WOMEN WITH PREVIOUS PREGNANCIES WHO HAD PREVIOUS TOXEMIA
White	130	45	32.6	7.7	15.6
Negro	157	37	35.2	7.6	21.6
Total	287	82	33.7	7.7	18.3

*Subsequent Eclampsia.*—There were eighteen subsequent attacks of eclampsia in seventeen white women and nine attacks in nine Negro women. The incidence of repeated eclampsia was 4.8 per cent. Thirteen and eight-tenths per cent of the women with subsequent pregnancies had eclampsia twice and one had eclampsia three times.

The old idea that eclampsia is never repeated has been disproved many times, but Dieckmann<sup>4</sup> says he has never seen a case, and Stander<sup>3</sup> says it rarely recurs. Peters,<sup>13</sup> however, reports eclampsia seven times in one patient, and six times in another. Greenhill<sup>2</sup> and Dieckmann<sup>4</sup> give the average rate of recurrence as 10 per cent. Page and Cox<sup>14</sup> from collected statistics found an incidence of 10.5 per cent. Other authors<sup>2, 12-17, 19, 26-31</sup> give rates of recurrence varying from 1.7 per cent to 21 per cent.

Stander<sup>3</sup> reports the usual incidence of eclampsia to be 0.15 per cent. Dieckmann<sup>4</sup> says the rate of occurrence in the United States is 0.66 per cent. Therefore the incidence of repeated eclampsia in this series is from seven to thirty-two times as great as in eclampsia in the general population.

*Previous Pregnancies.*—Previous to the original attack of eclampsia, there had been 287 pregnancies in 82 women. Thirty-two and six-tenths per cent of the white women and 35.2 per cent of the Negroes had had one or more previous pregnancies.

Of these pregnancies, in at least 22, or 7.7 per cent, there was a history of toxemia. The incidence was essentially the same in white and Negro pregnancies, 7.7 per cent and 7.8 per cent, respectively. On the other hand, 15.6 per cent of the white multigravidas and 21.6 per cent of the Negroes had at least one previous episode of toxemia. This is approximately the general incidence of toxemia.<sup>3, 4, 24, 25, 32</sup> These figures, of course, are no more reliable than those on subsequent toxemia; probably less so because of the time elapsed.

*Mortality.*—Twenty-seven patients died during the period of follow-up. Two white and two Negro women died of eclampsia, an incidence of 14.5 per cent. Two white and three Negroes died of some manifestation of hypertensive cardiovascular disease, 18.5 per cent. One white woman and two Negroes died of chronic glomerulonephritis, or 14.8 per cent of the total mortality. Three cases of pulmonary tuberculosis, one case of postoperative heart failure after a leg amputation in a diabetic, one stab wound, one cancer of the breast, one cancer of the larynx, one case diagnosed as nonspecific diarrhea, one thyrotoxicosis, one pneumonia post partum, one case of asphyxiation, and three cases undiagnosed accounted for the rest of the mortality. There may have been other deaths during this time, but if so they occurred outside of this state.

TABLE IV. DEATHS DURING THE PERIOD OF FOLLOW-UP STUDY

	TOTAL NUMBER OF DEATHS	PER CENT DIED OF ECLAMPSIA	PER CENT DIED OF CARDIO- VASCULAR DISEASE	PER CENT DIED OF CHRONIC GLOMERULO- NEPHRITIS	PER CENT DIED OF OTHER UNRELATED CAUSES
White	11	18.2	18.2	9.1	45.5
Negro	16	12.5	18.75	18.75	50.0
Total	27	14.5	18.5	14.8	47.8

*Subsequent Hypertension.*—Twenty-two white women and twenty-five Negroes were found to have a blood pressure of 140/90 or more at the time of follow-up examination. Those with either a systolic or a diastolic pressure in this range were included. Five patients with a blood pressure of 140/80 and two whose blood pressure was 140/70 were thereby included. It is quite possible

Finally, the importance of an adequate fluid balance is evidenced by the fact that when the patients were given more fluid or when 5 per cent glucose in water, intravenously, was added to the treatment, the diuresis increased markedly. This low concentration of glucose has replaced entirely the hypertonic solution formerly used in this department, following the study of Peterson, Goodwin and Finland,<sup>17</sup> Maddock,<sup>18</sup> and Winslow.<sup>19</sup> It has proved to be a potent adjunct in promoting diuresis.

The addition of magnesium sulfate to the veratrum viride seemed to be of real value. Less veratrum viride was required to obtain the same blood pressure fall when both drugs were administered simultaneously. Consequently, there was less nausea and vomiting and the urinary output increased despite the fact that the blood pressure and pulse rate were maintained at lower levels.

The urea clearance test was of no help in detecting any impairment of kidney function as the result of the treatment with veratrum viride because the variations were similar to those encountered in normal individuals.

Although this series of cases is small, the uniformity of results permits us to conclude that the slight and transitory decrease in urine volume following the use of veratrum viride does not endanger the life of the patient in any way. It can possibly be explained by a relative and transitory hemostasis due to a sudden fall in blood pressure aggravated by the vomiting and profuse diaphoresis.

### Summary

1. Eight pre-eclamptic, two eclamptic, three hypertensive and four normal pregnant patients were studied in control, veratrum viride, and combined periods.

2. The following changes were observed:

a. Normal pregnant patients showed no alteration in urine volume or blood pressure following the administration of veratrum viride.

b. Pre-eclamptic and hypertensive patients showed a slight decrease in the hourly urine volume following large doses of veratrum viride. A compensatory polyuria occurred thereafter, maintaining the total output for both periods in the same proportion.

c. No decrease in the urine volume was observed in the combined period.

3. The urea clearance test showed oscillations which were considered within the range of normal variability of the test.

4. A possible correlation between the variation in urine volume and the fall in blood pressure and pulse rate is discussed.

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between 40 and 49 years of age. Hypertension is more common in the Negro race. Schultze and Schwab<sup>40</sup> report that it is 2.5 times more frequent in Negroes than in whites, and 1.5 times more frequent in Negro women than in Negro men. Adams<sup>41</sup> says that the average blood pressure is 7 points systolic and 4 points diastolic higher in Negro men than in white men. According to mean age and race, therefore, we find little, if any, increase in hypertension among our patients, judging from the figures above. However, when we divide our cases into age groups, we find a definitely higher percentage of hypertensives among the younger women. There is certainly no increase in the older age groups.

TABLE VI. MEAN AGE OF HYPERTENSIVE GROUP AND INCIDENCE OF HYPERTENSION AT DIFFERENT AGES

	MEAN AGE	PER CENT WITH HYPER- TENSION 30-39 YEARS	PER CENT WITH HYPER- TENSION 30-39 YEARS	PER CENT WITH HYPER- TENSION 40-49 YEARS	PER CENT WITH HYPER- TENSION 50 YEARS-ABOVE
White	43.7	2.4	16.7	29.6	62.5
Negro	35.2	14.5	31.1	66.6	50.0
Total	39.8	8.9	22.5	41.0	60.0

*Proteinuria.*—Six of the women with hypertension, or 12.8 per cent, were found to have at least a trace of albumin in their urine at one examination. In those without hypertension, four patients, or 2.6 per cent, showed proteinuria. These figures are of little real value since about half the examinations were made on voided specimens. However, the incidence among the hypertensives is not high, as many of them were old severe cases with concomitant nephrosclerosis, and certainly the incidence in the nonhypertensives is negligible.

*Comparison of Subsequent Pregnancies Among Those With and Without Hypertension.*—

There were 106 subsequent pregnancies in 34 women in the hypertensive group and 459 pregnancies in 154 women of those found to have normal blood pressure at follow-up. Seventy-two and three-tenths per cent and 78.6 per cent of women in each group, respectively, had at least one subsequent pregnancy.

Among the women with hypertension there was an incidence of abortion or stillbirth of 17.0 per cent. The incidence in the nonhypertensive group was 24.2 per cent. It is surprising that the fetal mortality should be higher in the latter group, as hypertensive cardiovascular disease in itself, without superimposed toxemia, is supposed to cause a high fetal mortality.<sup>4, 24, 42</sup> Sharkey and Hess,<sup>43</sup> however, also found no increased mortality in their hypertensive patients, and as mentioned previously, these figures must be taken with some reservation.

Thirty-two and one-tenth per cent of these pregnancies were complicated by toxemia in the hypertensive group, as were 36.8 per cent in those with normal blood pressure. Fifty-two and nine-tenths per cent and 57.1 per cent of women in each group, respectively, had at least one toxemic pregnancy. Although this is in line with the above findings, and tends to confirm them, these figures are even more surprising, as hypertension is generally accepted as one of the causative factors in toxemia.<sup>4, 24</sup>

There were four subsequent attacks of eclampsia in four patients among those found to have hypertension, and twenty-two cases in twenty-one women in the group without subsequent hypertension, an incidence of recurrence of 3.8 per cent and 4.8 per cent in the two groups, respectively. These figures, in contrast to those concerning toxemia and abortion, may be presumed to be accurate, as no woman is likely to forget an attack of eclampsia, and, in addition, most of them were hospitalized in this institution. This also tends to confirm the approximate accuracy of the above questionable data.

that they did not have hypertensive cardiovascular disease. Since in many cases only one blood pressure reading was made, probably others are included who should not have been. Three patients known to be hypertensive before their attack of eclampsia were excluded, as were one with thyrotoxicosis, thirteen who were in the last trimester of pregnancy at the time, and six known to have chronic glomerulonephritis or chronic pyelonephritis. The reasons for exclusion of the last group will be discussed below. The incidence of hypertension according to these standards was 21.4 per cent, 17.7 per cent in the white women and 26.0 per cent in the Negroes.

Different investigators have used different standards to determine hypertension, and of course the number of patients and the periods of time elapsed have varied, so comparison to other follow-up studies is difficult. Teel and Reid<sup>9</sup> followed 80 eclamptics 7.6 years. Using a systolic pressure of 150 as a standard, they found an incidence of 27.5 per cent hypertension. However, among those known to have had normal blood pressure previous to the eclampsia, the rate was only 10 per cent. Reid and Teel,<sup>33</sup> studying pre-eclampsia, found hypertension in 51 per cent of cases in which the previous blood pressure was not known. Among those known to have been without previous hypertension, the incidence was 21 per cent after mild pre-eclampsia and 2 per cent after severe. Chesley, Somers, and Vann,<sup>10</sup> in a recent study of 240 eclamptics followed one to eight years, found a subsequent blood pressure of 140/90 or more in 15 per cent. Light recently found 30.1 per cent hypertension in a follow-up of nonconvulsive toxemic patients. Dexter and Weiss<sup>24, 25, 34</sup> say 25 per cent of patients have hypertension after toxemia. Page and Cox<sup>14</sup> report that in 13,000 cases of toxemia collected from the literature, the incidence is 43 per cent. Dieckmann and Brown<sup>4, 16, 31</sup> report an average of 27 per cent subsequent hypertension after eclampsia and 34 per cent after nonconvulsive toxemia from the literature. In their own series they had an incidence of 37 per cent and 40 per cent after eclampsia and pre-eclampsia, respectively. Stander<sup>3</sup> said that from one-fifth to one-tenth have residual vascular damage. Other authors<sup>5, 11, 15, 17, 18, 20, 24, 33-38</sup> give figures varying from 13 per cent to 63.4 per cent.

TABLE V. INCIDENCE OF HYPERTENSION FOUND AT FOLLOW-UP. ALL PATIENTS WITH A SYSTOLIC PRESSURE OF 140 OR MORE, OR A DIASTOLIC PRESSURE OF 90 OR MORE, ARE CLASSIFIED AS HYPERTENSIVES

	PATIENTS WITH B.P. 140/90 OR MORE		PATIENTS WITH B.P. LESS THAN 140/90	
	NO.	PER CENT	NO.	PER CENT
White	22	17.7	116	82.3
Negro	25	26.0	80	26.0
Total	47	21.04	196	21.4

*Subsequent Hypertension According to Age.*—The average age of the women with hypertension in this series was 39.8 years, 43.7 years for the white patients and 35.2 years for the Negroes. When we break this down into age groups, we find the incidence of hypertension from 20 to 29 years to be 2.4 per cent in the white women and 14.5 per cent in the Negroes. In the 30 to 39 age group we find 16.7 per cent and 31.1 per cent for white and Negro. The percentage from 40 to 49 years was 29.6 and 66.6, respectively. In those over 50 years of age, five white women and one Negro had hypertension, or 62.5 per cent and 50 per cent. The total incidence of hypertension was 8.9 per cent, 22.5 per cent, 41.0 per cent, and 60.0 per cent, respectively, for the four age groups. Of course the number in each group is much too small to be of any statistical value, but the results do show the general trend.

Master, Marks, and Dack,<sup>39</sup> in 6,366 women, mostly white workers in industry, found a blood pressure of 140/90 or more in 39.27 per cent of women

Twenty-seven women died during the follow-up period. Four (14.5 per cent) died of eclampsia, five (18.5 per cent) of some manifestation of cardiovascular disease, and four (14.8 per cent) of chronic glomerulonephritis.

Forty-seven, or 21.4 per cent, were found to have a blood pressure of either 140 systolic or more or 90 diastolic or more. The incidence in the white women was 17.7 per cent and in the Negroes 26.0 per cent. Some of these were single readings.

The mean age of those women found to have hypertension was 43.7 years for the white women and 35.2 years for the Negroes. For women in this age group, the incidence is not significantly high. However, among the younger women hypertension was found more frequently than would be generally expected. Eight and nine-tenths per cent of those from 20 to 29 years old had an elevated blood pressure.

The incidence of abortion or stillbirth and of toxemia was found to be lower in the subsequent pregnancies of those found to have hypertension than in those with normal blood pressure. This was also true in those pregnancies preceding the original attack of eclampsia in these women.

Now, what do these data tend to show in regard to the relationship of eclampsia to cardiovascular-renal disease?

As stated above, although it has been said that eclampsia causes chronic nephritis, six patients diagnosed as having chronic glomerulonephritis or chronic pyelonephritis have been omitted in figuring the incidence of hypertension in this series.

Many authors<sup>12, 21, 22, 23, 44, 45</sup> have reported an incidence of chronic nephritis up to 74 per cent in follow-up studies of eclampsia and toxemia. However, Dieckmann<sup>4, 16, 31</sup> and Dexter and Weiss<sup>24, 25, 34</sup> have pointed out that in most cases this diagnosis was made on hypertension and/or proteinuria alone. Although Acosta-Sison<sup>46</sup> reports the pathological lesion of eclampsia as a nephritis, and Peters<sup>13</sup> and Addis<sup>47</sup> state that eclampsia is identical with acute glomerulonephritis, Bell<sup>48</sup> and Herrick and Tillman<sup>11</sup> have proved that the kidney lesions found both in acute eclampsia and in follow-up studies are of a degenerative rather than an inflammatory nature, that is, nephrosclerosis rather than glomerulonephritis. The follow-up studies of Browne and Dodds<sup>20</sup> and Teel and Reid<sup>9, 33</sup> bear this out. Dieckmann<sup>4</sup> and Dexter and Weiss<sup>24</sup> conclude that the preponderance of evidence leaves no doubt that eclampsia is not a nephritis, nor does it cause chronic nephritis.

Therefore, since the only relationship that chronic glomerulonephritis bears to eclampsia is that of a possible contributory causal factor, those cases were excluded. Obviously, chronic pyelonephritis cannot result from eclampsia per se.

But does eclampsia leave behind some residual vascular damage? Does it result in subsequent hypertensive cardiovascular disease?

Dexter and Weiss,<sup>24, 25, 34</sup> who have done a great deal of careful work on the subject in the last few years, are convinced that toxemia often causes irreparable damage. Greenhill,<sup>2</sup> Stander,<sup>3</sup> Gibberd,<sup>23</sup> Harris,<sup>44</sup> Young,<sup>7, 8, 19, 30</sup> Peckham,<sup>12, 38, 45</sup> Peters,<sup>13</sup> Herrick and Tillman,<sup>11</sup> and many others are proponents

TABLE VII. COMPARISON OF SUBSEQUENT PREGNANCIES IN THE HYPERTENSIVE AND NONHYPERTENSIVE

	NUMBER OF SUBSE- QUENT PREG- NANCIES	PER CENT OF WOMEN WHO HAD SUBSE- QUENT PREG- NANCIES	PER CENT OF SUB- SEQUENT PREG- NANCIES WHICH RESULTED IN STILL- BIRTH OR ABORTION	PER CENT OF SUB- SEQUENT PREG- NANCIES WHICH WERE TOXEMIC	PER CENT OF WOMEN WITH SUB- SEQUENT PREG- NANCIES WHO HAD SUBSE- QUENT TOXEMIA	PER CENT OF SUB- SEQUENT PREG- NANCIES WHICH WERE ECLAMPTIC	PER CENT OF WOMEN WITH SUB- SEQUENT PREG- NANCIES WHO HAD SUBSE- QUENT ECLAMPSIA
Hyper- tensive	106	72.3	17.0	32.1	52.9	3.8	11.8
Nonhyper- tensive	459	78.6	24.2	36.8	57.1	4.8	13.6

*Comparison of Previous Pregnancies.*—Previous to the original attack of eclampsia in this study, there were 82 pregnancies in 21 women among the hypertensives, and 205 in 61 women in those with normal blood pressure at follow-up. Of these pregnancies, 7.3 per cent were toxic in the first group and 7.8 per cent in the second. Among those who had previous pregnancies, 19.0 per cent of the women without hypertension and 18.0 per cent of those with subsequent hypertension had at least one pregnancy complicated by toxemia.

TABLE VIII. COMPARISON OF PREGNANCIES OCCURRING PRIOR TO ORIGINAL ATTACK OF ECLAMPSIA IN THE HYPERTENSIVE AND NONHYPERTENSIVE GROUPS

	NUMBER OF PREVIOUS PREGNANCIES	PER CENT OF WOMEN WHO HAD PREVIOUS PREGNANCIES	PER CENT OF PREVIOUS PREGNANCIES WHICH WERE TOXEMIC	PER CENT OF WOMEN WITH PREVIOUS PREG- NANCIES WHO HAD PREVIOUS TOXEMIA
Hypertensive	82	61.8	7.3	19.0
Nonhypertensive	205	31.1	7.8	18.0

Summary and Conclusions

In summarizing the above data we describe 243 cases of eclampsia followed for an average of 12.3 years. The mean age was 32.6 years at this time.

There were 565 subsequent pregnancies in 188 women, of which 22.9 per cent resulted in either stillbirth or abortion. This fetal mortality is almost twice as great as that expected in general.

Of these pregnancies, at least 203, in 106 women, were complicated by toxemia, an incidence of 36.1 per cent. Fifty-six and four tenths per cent of the patients have had at least one toxemic pregnancy. This is four to six times the general rate of occurrence.

Eclampsia recurred 27 times. One woman had two subsequent attacks. The incidence of repeated eclampsia was 4.8 per cent, or from seven to thirty-two times greater than the usual rate of occurrence as reported by various authorities.

Previous to the original attack of eclampsia, there were 287 pregnancies in 82 women. Of these, 7.7 per cent were toxemic. This is approximately the usual incidence of toxemia.

pressure than in those with hypertension is of little statistical significance, but, on the other hand, these apparently normal women have been followed for an average of 12.3 years. They have had an average of three pregnancies each, of which 36.8 per cent were toxemic. One would expect that if they had had a latent or potential hypertensive cardiovascular disease, it would have become clinically evident by this time.

In conclusion, it may be said that according to the results of this study, eclampsia is a specific disease of pregnant women. It is not a manifestation of chronic nephritis, nor of hypertensive cardiovascular disease, although either of these conditions may precede the attack of eclampsia and possibly render the patient more susceptible to toxemia. Neither does eclampsia nor nonconvulsive toxemia cause chronic nephritis or hypertensive cardiovascular disease. Patients who have once had eclampsia or pre-eclampsia are more likely to have subsequent toxemia and a high incidence of stillbirths and abortions, following the "toxemic sequence" of Young.<sup>7, 8, 10, 30</sup> This is not, however, because of some constitutional weakness "or morbid influence," as he suggested, not because they are essential hypertensives, as Dieckmann<sup>4</sup> states, nor is it because the first attack leaves them more susceptible; but rather, it is because the same etiological factors—environment, diet, etc., are very likely to remain more or less constant and to provoke the same results in subsequent pregnancies.

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of the theory that there are sometimes or always residuals. Teel and Reid<sup>9, 33</sup> conclude that eclampsia causes little damage but that nonconvulsive toxemia perhaps causes more.

On the other side of the argument, Dieckmann<sup>4, 49</sup> and Dieckmann and Brown<sup>16, 31</sup> have probably done more work than anyone else in this country. They are equally convinced that the true toxemias of pregnancy cause no permanent damage. Chesley, Somers, and Vann,<sup>10</sup> Light,<sup>50</sup> McClellan, Strayhorn, and Densen,<sup>35</sup> and Browne and Dodds<sup>20</sup> have all presented follow-up studies which they interpret as confirming this viewpoint. Icenhour, Kuder, and Dill<sup>51</sup> examined 900 nulliparous women and 900 parous women and found no more hypertension in the latter group. Barnes and Browne<sup>52</sup> made a similar study of 915 nulliparous and 1,044 parous women with similar results. Theobald<sup>53</sup> examined the death reports for England and Wales for the years 1911-1920 and found that the incidence of death from arteriosclerosis and Bright's Disease was higher in single than in married women. However, Golden, Dexter, and Weiss<sup>25</sup> cast some doubts on the statistical significance of his figures.

This study indicates that eclampsia does not cause hypertensive cardiovascular disease, although as indicated by the higher incidence found in the younger women, it may aggravate a pre-existing condition, causing it to be clinically evident at an earlier age.

Although only cases of eclampsia were included in this study it is felt that the same conclusions may be drawn in regard to pre-eclamptic toxemia as well. The work of Dexter and Weiss,<sup>24, 25, 34</sup> Peckham,<sup>38</sup> Teel and Reid,<sup>9</sup> Harris,<sup>44</sup> Gibberd,<sup>23</sup> Young,<sup>7, 8</sup> and others is interpreted as indicating that the duration of the toxemia is the important factor in causing permanent vascular damage. They feel that the severity of the attack is of secondary significance. But, on the other hand, although the word eclampsia means "to flash forth," implying a condition of sudden onset, it is well known as Greenhill<sup>2</sup> and Stander<sup>3</sup> have both pointed out, that in most cases convulsions are preceded for some time by the signs and symptoms of toxemia. Although eclampsia may occur occasionally, with apparently no premonitory signs, it is nearly always the end result of a long-standing and neglected toxemia. It seems reasonable, therefore, that if pre-eclampsia leaves residual damage, eclampsia should do so as well, and that if eclampsia causes no permanent vascular changes, then neither should pre-eclampsia.

One reason for the high incidence of subsequent hypertension found in many follow-up studies of nonconvulsive toxemia is, as Dieckmann,<sup>4</sup> Dexter and Weiss,<sup>24, 25, 34</sup> and Teel and Reid<sup>9, 33</sup> have brought out, that many cases diagnosed as mild pre-eclampsia are, in reality, cases of essential hypertension to begin with.

What is the significance of the relative incidence of toxemia in the hypertensive and nonhypertensive groups? Dieckmann<sup>4</sup> believes that true toxemia seldom if ever recurs. He says that those patients who have repeated toxemias are actually cases of essential hypertension. The information gained from this study certainly does not bear out this belief. Of course the finding of a slightly higher incidence of toxemia in those patients with a normal subsequent blood

tension to indicate a predisposition to severe hypertensive vascular disease. When such women again become pregnant, environmental and controllable causes of the original eclampsism should be searched for and eliminated.

DR. R. B. NICHOLLS, Norfolk, Va.—We in private practice are faced with the seriousness of eclampsia on too frequent occasions. This paper is a definite contribution to the general knowledge which is accumulating to help us manage more satisfactorily the severest of the toxemias of pregnancy.

One cannot read the vast amount of literature on eclampsia and be unimpressed by the effect that diet, hygiene, and economic factors have on the incidence of eclampsia.

In a recent survey of eclampsia at the Norfolk General Hospital, over an eight-year period extending backward from 1948, it was shown that eclampsia occurred 26 times in 10,390 deliveries, or .025 per cent. One of the interesting points that I found was that nine cases of eclampsia occurred during the war year 1944. The two years on either side of 1944 showed that there were only three cases in 1943 and one case in 1945. One naturally questions the reason for the sudden rise of eclampsia in that single year. It appears that this high incidence in 1944 could be a deficiency in protein in diet as a result of difficulty in obtaining meat due to rationing. It could be partly an emotional effect of the husbands being in the service or over seas, and it could be partly a result of financial and economic inability to supply the proper foods for the diet.

Of these 26 eclamptics during that eight-year period, 20 had prenatal care and 6 had no prenatal care. There were 14 cases in private patients and 12 cases in clinic patients. Three deaths occurred among the 26 patients, of whom two had had no prenatal care. One could hardly arrive at conclusions from such a small group of patients, but apparently the lack of prenatal care has more effect upon the severity and fatality of the eclampsia than on its occurrence.

Evidence is building up to show that eclampsia as such can occur more than once in the same individual in subsequent pregnancies. A patient who has once had eclampsia, particularly if it is with her first baby, is concerned as to whether or not her chances are increased of having another eclamptic pregnancy. It is not always possible to tell the patient whether she may develop eclampsia or not, but there are several things which, if recognized, will help in determining the prognosis for the patient.

First, if the patient is of an older age group, that is, from 30 years on upward, repeat toxemias are more likely to occur.

Second, if the eclampsia occurred during the first pregnancy her chances are less for recurrence of toxemia than if it occurred during subsequent pregnancies. Leon Chelsey at the Margaret Hague Hospital quotes 42 per cent chance of recurrence after the first pregnancy as against 62 per cent chance in subsequent pregnancies.

Third, the duration of the toxemia in days and weeks seems to have importance in the prognosis for future pregnancies. The longer the duration of the toxemia the greater the repeat incidence of toxemia. Quoting Chelsey again, "If the toxemia was for one week or less there is a 20 per cent chance; one to two weeks, 41 per cent chance; two to three weeks, 50 per cent chance; and more than three weeks, 83½ per cent chance of repeat toxemia."

Fourth, the more promptly the blood pressure and urine return to normal after delivery in the eclamptic patient the more favorable the outlook for future pregnancies. If the blood pressure and urine are normal by the tenth day she has a 22 per cent chance of recurrence. If either the blood pressure or the urine are normal after the tenth day there is nearly a 60 per cent chance of repeating toxemia, quoting Chelsey.

Fifth, the more heavily built the patient is, the more likely she is to have another toxemia.

DR. JOHN CROSS, Atlanta, Ga.—The question of the incidence of permanent vascular disease following toxemia of pregnancy is a controversial one. There are many groups of statistics, from clinics in all sections of the country, which will confirm either side of the

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## Discussion

DR. LESTER WILSON, Charleston, S. C.—Reports of autopsies upon women who have died some years after apparently recovering from eclampsia are few and are concerned chiefly with changes in the kidneys. In one patient who died seven years after having had eclampsia many glomeruli were found to show focal scars which Bell interpreted as having resulted from the eclampsia. Kellar and Baird and Dunn, and others, found no significant changes in kidneys of women, autopsied one or more years after the original eclampsia, who did not have hypertension. Patients with persistent postpregnancy hypertension following eclampsia or pre-eclampsia usually show at autopsy the nephrosclerosis characteristic of hypertensive vascular disease and no lesion characteristic of eclampsia. Bell's interpretation of focal glomerular scarring as a post-eclamptic renal lesion has therefore never been substantiated.

From the clinical viewpoint there is also difference of opinion, as the authors have pointed out. Even with the knowledge of this controversy, I am not fully convinced that eclampsism does not damage the vascular-renal system in normal women without inherent predisposition to hypertensive vascular disease. The authors' report of an unusually high incidence of hypertension in the young groups tends to bear this out. I have some objection to the paper itself in attempting to prove so important a point as this. No pre-pregnancy hypertension figures are given; the age at onset of hypertension in relation to age at time of pregnancy is not given; and, in some instances, only one blood pressure was taken. In other words, there is no attempt to individualize patients and to show what changes took place in them as individuals. Where this has been done, as Dexter and Weiss have shown, the inference has been drawn that eclampsism does cause vascular-renal damage in more women than would have had such damage had they not developed eclampsism. I heartily agree that eclampsia tends to repeat itself in patients whose environment continues to predispose to eclampsia, but I do not believe that this is the whole story.

Studies of this sort should emphasize to us the importance of careful follow-up on patients who have had pre-eclampsia or eclampsia. The vascular and renal systems should be carefully examined for evidence of postpregnancy hypertensive vascular disease or a predisposition to this disease, before future pregnancies are advised. A careful family history of hypertension is valuable. Repeated blood pressure determinations and urinalyses, including search for casts as well as albumin, specific gravity, and renal function tests should be done. Funduscopic examination will rarely be of value unless there is definite hypertension. The cold pressor test has been used in patients with postpregnancy hyper-



## THE DIFFICULT GENITAL FISTULA; TEMPORARY DESCENSUS UTERI FOR RELIEF OF TENSION\*

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IT IS my intention to report the satisfactory use of some of the older and less desirable operations and to present a new method of using an equally ancient principle for the relief of tension on the sutured wound edges.

The basic principles of the management of the genital fistulas are well known and will not be reviewed here. The use of sulfonamides and antibiotics and the new knowledge of physiologic requirements for optimum wound healing have done much to simplify our task but we still have the problem of reducing tension on the wound edges in the large fistulas and in those with extensive scar tissue.

In 1845 Jobert de Lamballe<sup>1</sup> made a transverse incision anterior to the cervix (the "crossbar" of our "inverted T") to free the bladder from the cervix. His pupil, Gustav Simon,<sup>2</sup> used tension-relieving sutures instead of this incision. Sims<sup>3</sup> and Emmett<sup>4</sup> used relaxing incisions combined with massage and dilatation of the vagina with plugs and tampons in preoperative preparation to reduce tension on the suture line.

The anterior surface of the partially prolapsed cervix has been drawn down under the fistula and used to "patch" the defect. The corpus uteri has been interposed and sutured under the defect as in the Watkins' operation by Frank.<sup>5</sup> Kelly<sup>6</sup> in a case of retroversion-flexion brought the corpus out through a cul-de-sac incision and used it for this purpose. In another case he did not hesitate to cut the bladder entirely away from the cervix. No attempt was made to close the resulting defect in the vaginal wall, it being allowed to granulate. Kelly also made extensive use of inverted flaps of the vaginal wall to close fistulas with minimum tension.

We have recently been confronted with the problem of an unusually large vesicourethrovaginal fistula. The entire trigone plus the posterior two-thirds of the urethra were involved (Fig. 1). The ureteral orifices opened on the posterior edge of the fistula. It seems that an operation for cystocele had been performed. A piece of vaginal wall which inadvertently reached the pathologist was reported to be 4 by 5 cm. in size. Troublesome bleeding at the time of operation was controlled by tight packing of the vagina and numerous transfusions. When the pack was removed, the bleeding recurred and the patient was packed again. When this pack was removed, the catheter tip was found in the vagina and complete incontinence ensued. Late massive hemorrhage occurred on the eighth postoperative day and the patient was rehospitalized in shock. She was again packed tightly and when this pack was removed, renewed bleeding led the attendant to attempt closure of the fistula and control of the bleeding by deep blind suturing. This undoubtedly contributed materially to the large size of the fistula.

\*Read at the annual meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Va., Feb. 10 to 12, 1949.

question. The authors call attention to the wide difference of opinion among other men, each opinion based on statistics that tend to support it. A very critical analysis of all statistical data should be made in order to make the deductions of real value.

In the present series of 243 eclamptics, it would be interesting to know if this condition had developed in women with previously normal cardiovascular renal systems. A table giving the number of eclamptics, and the year each case occurred, would help in the follow-up study of cases. It would be advisable to include the incidence, the severity, and the duration of the pre-eclampsia in these cases. These are important and variable factors which have received a great deal of attention by several writers in their evaluation of posttoxemic vascular and renal complications.

The number of Negro patients and the number of white patients in the hypertensive and nonhypertensive groups is not given. There is enough difference in the incidence of toxemia in the two groups to justify parallel series throughout the study. The combined statistics, covering both white and Negro patients, give data that cannot be compared accurately with any other reports.

A diagnosis of hypertension, often borderline, can be very misleading if it is based upon one blood pressure reading not preceded by a few minutes' rest. The finding of a higher incidence of subsequent toxemia in the nonhypertensive than in the hypertensive group is certainly unusual. Since the term toxemia can be very inclusive, I think that a definition of what is meant by subsequent toxemia would be necessary in analyzing the results. The conclusion that repeat toxemia is the result of some etiological factor such as environment, diet, etc., and not the manifestation of chronic glomerulonephritis or a premature cardiovascular change, cannot be disproved. However, I do not think the statistics as given are sufficiently conclusive to establish environment, diet, etc., as the probable etiologic factors.

It seems that from all the work done during a considerable period of time on the subject of toxemia in pregnancy, there are only a few facts that stand out. These are:

Toxemia manifests itself during the latter half of pregnancy as an acute vascular disorder characterized by a generalized angiospasm causing anoxemia and accompanied by an increase in the permeability of the vessel walls and by hypoxia to some of the tissues, depending on the anatomical distribution of the vascular tree.

These clinical findings and a few years of experience observing a large number of cases of toxemia in pregnancy, mostly in the Negro race, have impressed me with the increased incidence of hypertension and nephrosclerosis following toxemia of pregnancy. The main contributing factors are: first, the duration of the disease; second, the age of the patient; and finally, the severity of the disease.

In closing, I want to thank Drs. Torpin and Bryan for giving us these statistical data on so large a series of eclamptics followed for such a long period of time. It is from such exhaustive studies as theirs that much data will be obtained to aid in determining the incidence and type of posttoxemic vascular and renal complications, if any.

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The author describes his experiences in the use of intrapelvic injection of penicillin through the cul-de-sac in selected pelvic inflammatory processes, acute and subacute, which had failed to respond to more or less routine chemotherapeutic treatment. He recommends usually an initial injection of 50,000 to 100,000 Oxford Units with repeated dosages totaling 300,000 to 2,000,000 Oxford Units. There is usually a rapid fall of temperature by the third day with early localization and resolution of the inflammatory processes. CLAIR E. FOLSOME.

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### Addendum

After this report had been submitted for publication, three additional cases of antepartum convulsive eclampsia were studied. All were comatose at the time of admission. Veratrum viride was administered intravenously in doses varying from 0.2 to 0.3 c.c. every hour. Fluid intake consisted chiefly of intravenous 5 per cent glucose in water.

Unfortunately, in all three cases, control periods were not obtained because of the serious condition of the patients and the necessity for immediate treatment. The following table outlines the data on these three patients:

NAME OF PATIENT TIME OBSERVED	MEAN B/P BEFORE TREAT- MENT	MEAN B/P AFTER TREAT- MENT	FLUID INTAKE (C.C.)	URINARY OUTPUT (C.C.)
M. F. 48 hours	210/120	130/82	5,100	3,300
G. R. 36 hours	180/110	120/60	4,200	2,950
L. U. 12 hours	220/102	130/70	3,000	2,700

The intravenous use of veratrum viride is now being extensively studied in this department and will form the subject of a future report.

At operation four months later, the tissues were found to be in good condition in spite of widespread scarring of the vagina and adequate mobilization was secured. The bladder and urethral defect could not be approximated longitudinally, so were closed transversely with interrupted sutures of No. 000 chromic gut. The vaginal wall also had to be closed transversely using No. 00 chromic gut interrupted sutures but fortunately the two suture lines were not superimposed. When the cervix was released at the end of the operation, the resulting tension caused two of the vaginal wall sutures to cut through. It appeared that a radical deep incision completely cutting the bladder away from the cervix would be necessary to reduce this tension. Rather than do this, the cervix was brought down to the introitus again and sutured there. A loop of large nylon was passed transversely through the cervix, then through the deep fascia over the ischiopubic rami and tied over the fourchette. The result was quite gratifying and prompt primary union occurred. Because of the discomfort to the patient who required frequent small doses of morphine for backache, the cervical anchoring suture was cut on the eighth postoperative day. Tension again developed but so slowly that although the vaginal wound edges separated slightly, granulation was sufficiently rapid to fill in the defect and good epithelization eventually occurred.

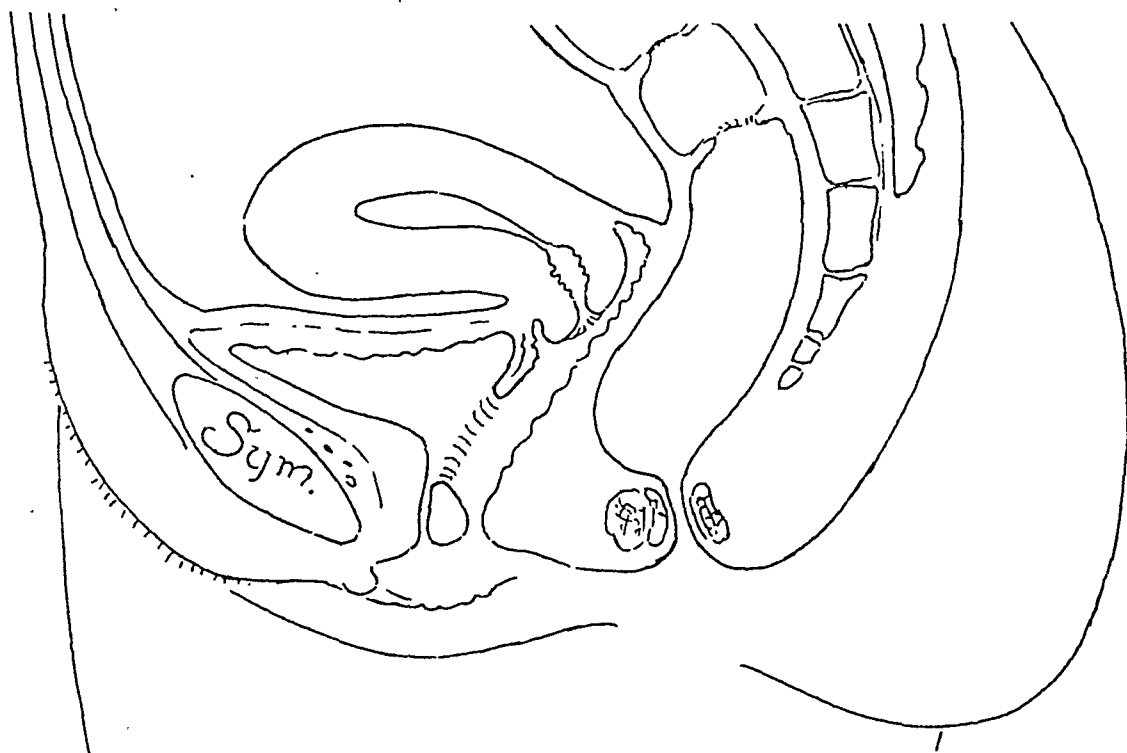


Fig. 1.

There was of course no urethral control and an Aldridge-Te Linde modification of the Stoeckel-Goebell-Frangenheim operation was performed three months later. The left external oblique fascial strip was rather flimsy but a badly scarred old midline incision prevented use of an anterior rectus strip. The result was excellent at first but stress incontinence developed. Six months later operation for removal of a large endometrial cyst of the ovary became necessary and at this time the left half of the Aldridge sling could not be identified. It apparently had completely atrophied. Again using the procedure of Te Linde, a strip of fascia lata was used successfully to replace the atrophied Aldridge loop (Fig. 3).

In consideration of the rather prompt recurrence of the tension on the vaginal suture line which followed release of the temporarily prolapsed cervix, I would not again use a single anchoring stitch but would use sutures on both

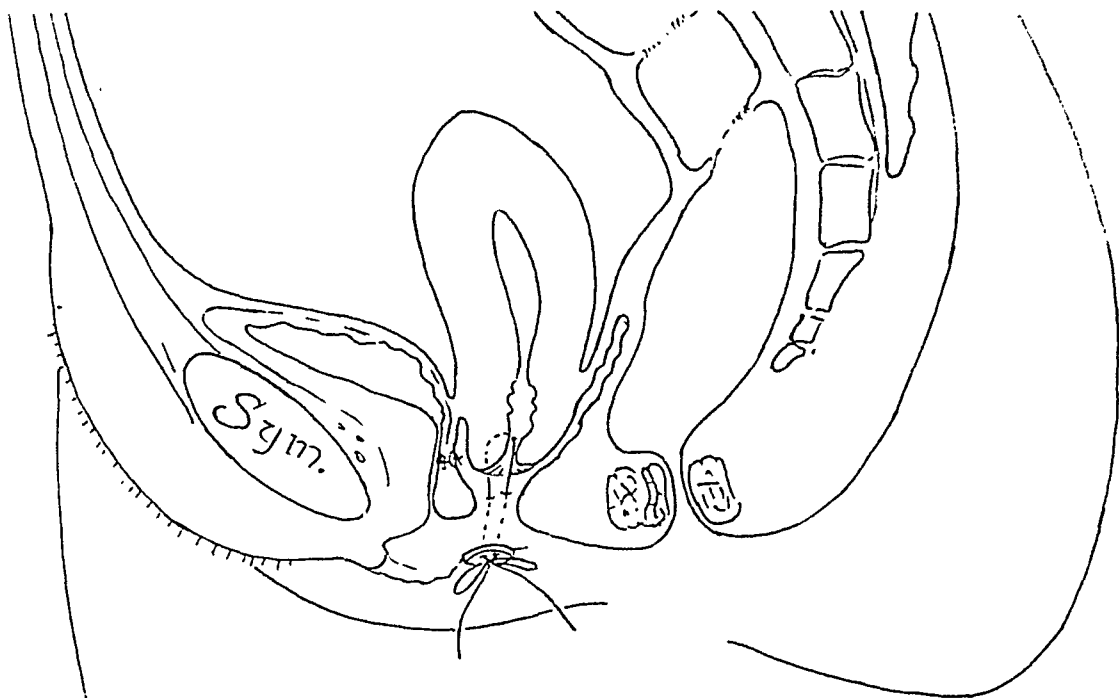


Fig. 2.

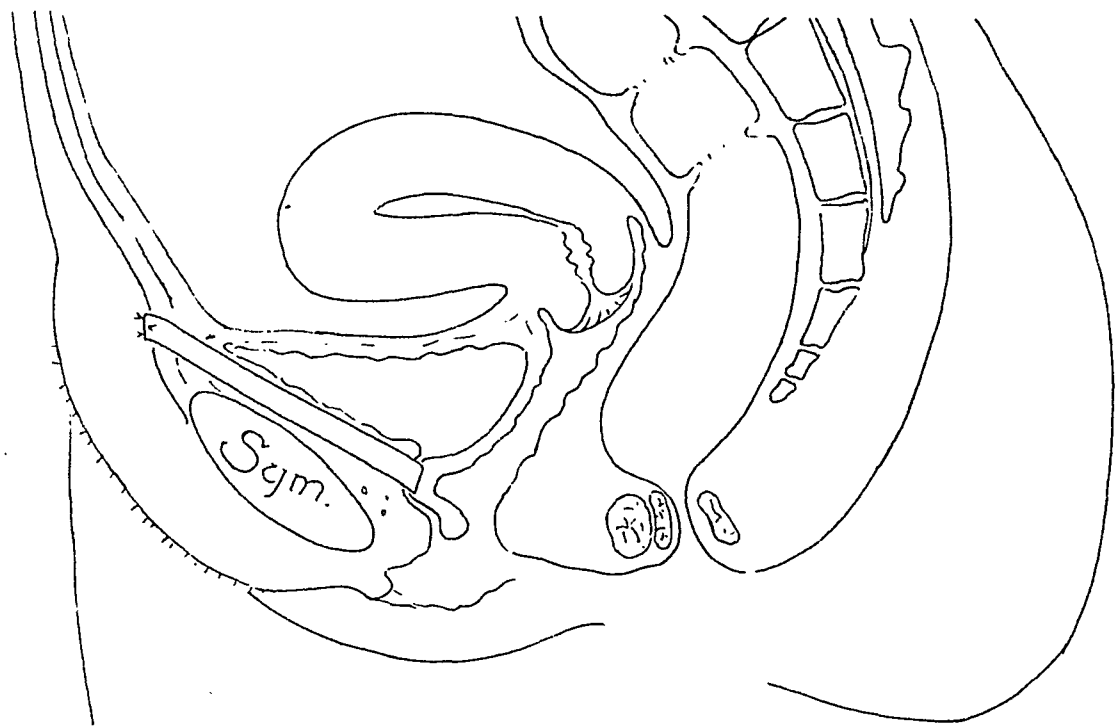


Fig. 3.

sides of the cervix passing through the fascia over the ischiopubic rami and tied over buttons in such a way that the sutures would be gradually lengthened and thus avoid possible disruption of the healing wound (Fig. 2).

Formerly, obstetric injuries furnished the greater portion of genital fistulas and surgery contributed largely through repeated operative failures to the difficulty of eventual management. At the present time better obstetrics results in fewer cases and these in turn have access to good surgery for their repair. In our own experience the most common causes of fistulas are radium-treated carcinoma of the cervix and the loss of tissue due to lymphopathia venereum. One of our most hopeless cases had both etiologic factors.

Management of the two groups differs widely. The tissues remaining after the lymphopathic process is arrested do not lend themselves well to surgery. They are friable, inelastic, and ischemic and the most satisfactory remedy for incontinence is diversion of the urine by transplantation of the ureters to the sigmoid if the disease has not damaged the rectum and/or anus too much.

A determined effort should be made to evaluate the status of the malignancy before any surgery is decided upon for if fistula in a cancer patient is due to malignant disease, the case of course is hopeless. There is, however, not an inconsiderable number of women whose cancer is apparently under control but who have fistulas which make them miserable. Perhaps most of the patients with such cases come to us after heavy radiation of Stage 2 carcinoma with extension to the vagina because it is axiomatic with us that nothing is worse than cancer even though genital fistula may rank a close second in the patient's estimation. It is only fair to confess that an occasional fistula presents itself in our clinic even though the technical problem in the use of radium does not explain it.

The vesicovaginal and rectovaginal fistulas in the radium-treated patient present a different problem from those resulting from obstetric and surgical injury. There is associated with the defect changes in the adjacent tissue: cicatrization, ischemia through radiation effect on blood vessels, fixation of the cervix and uterus through fibrosis, and not infrequently lower ureteral obstruction from periureteral fibrosis with resulting ureterectasis. This emphasizes the need for complete urologic study in all cases to differentiate ureteral blockade due to fibrosis from that due to extension of carcinoma to the ureter. This is best done by repeated dilatation, the latter not responding to such treatment while the former may do so. Many patients with irradiated carcinoma of the cervix have ureterectasis which does not lend itself well to transplantation, however, so attempt at relief from below should be made. In discussion of the management of this group of patients I will draw freely on the combined experience of Dr. John F. Denton and Dr. Calvin B. Stewart and myself at the Steiner Cancer Clinic.

We are frequently able to close a small fistula due to radiation with the usual methods, especially if estrogens are used locally for about ten days in an effort to vascularize the mucosa. We do not think this short course is contraindicated in spite of the theoretical danger of estrogen therapy in cancer patients. Often, however, we find that it is impossible to mobilize the tissues with any of the usual methods of counterincision, etc. For such fistulas high in the vagina Latzko's method may be used. It consists of excision of a cuff of vaginal mucosa about the fistula and suturing the anterior and posterior walls together. Obviously this cannot be done in the presence of a cervix or uterus which requires drainage but may be performed occasionally where the cervix and uterus, if present, have been virtually obliterated through irradiation. It is usually compatible with an active sex life but the other procedures to be discussed are not.

Large vesicovaginal or vesicorectovaginal fistulas may be treated by partial vaginectomy if the sphincters are intact (Figs. 4 and 5). This was first done by Simon<sup>2</sup> in 1848. We have not found it necessary to divert the fecal stream in such cases. These women seem to get along fairly well with a bladder that is in part lined with vaginal mucosa and the ones who have combined fistulas do

not seem to have much ill effect from the presence of feces in the bladder or urine in the rectum. Perhaps these women have suffered so greatly that they complain little of petty annoyances.

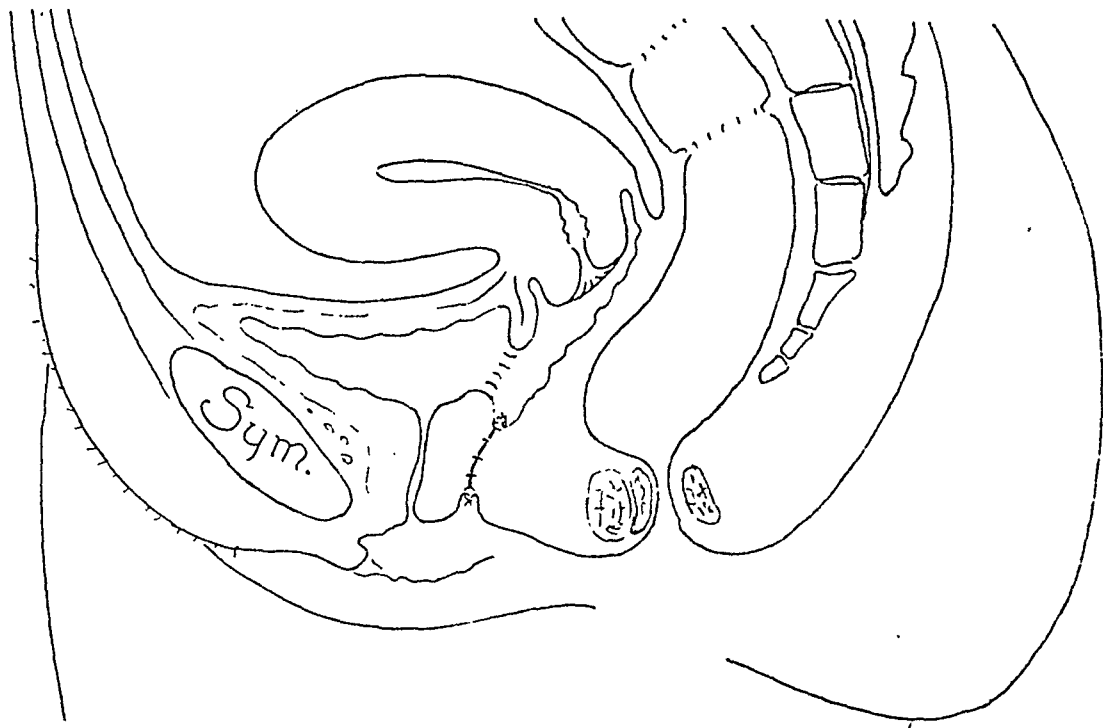


Fig. 4.

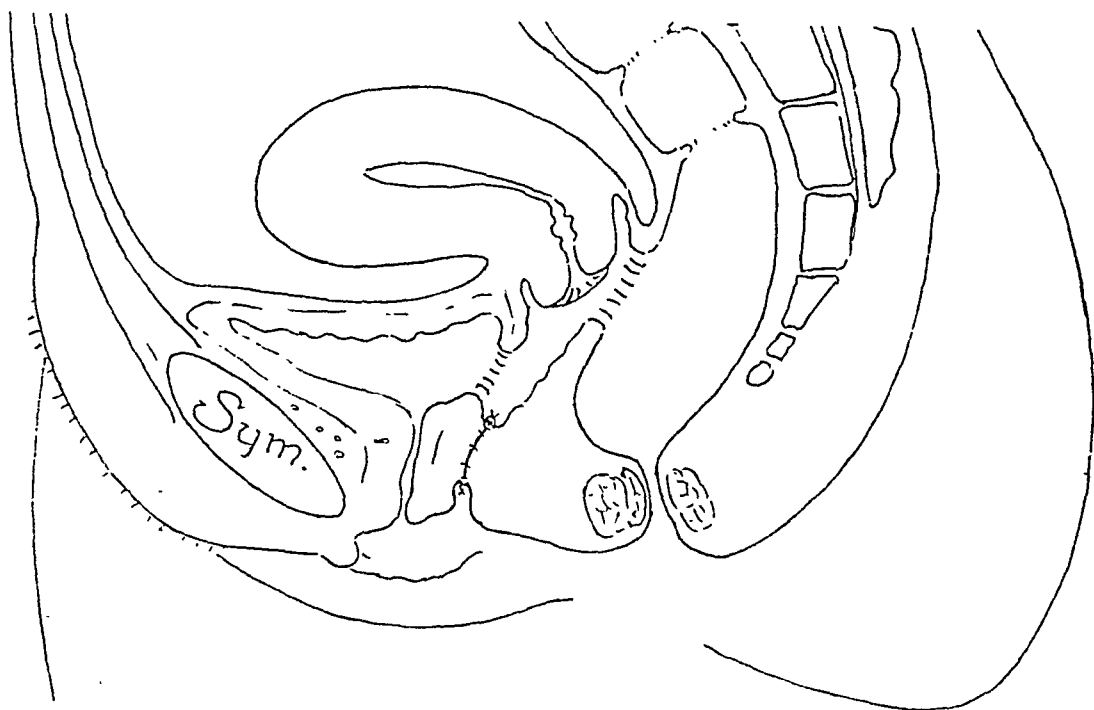


Fig. 5.

Occasionally vaginectomy may be applied to patients with extremely large fistulas. A patient with a Grade 1, Stage 2 carcinoma (extension to the upper vagina) was treated with 7,000 r. of x-ray and 8,000 mc. hr. of radium with

prompt regression but localized recurrence in the cervix and vagina eighteen months later. In spite of the heavy irradiation and the ischemic appearance of the tissues, it was apparent that surgery offered her only chance for salvage. She was apprised of the danger of fistula formation and accepted it. Radical hysterectomy and salpingo-oophorectomy with the removal of the upper third of the vagina was done. When examined seven days postoperatively preliminary to contemplated excision of the vagina from below, the upper half of the remaining two-thirds of the vagina was seen to be undergoing necrosis. Widespread sloughing occurred ten days later. Ninety days later the slough had completed and the ureteral orifices were seen on the posterior edge of the fistula. The remaining third of the vagina was removed. The bladder capacity rapidly improved and the patient is symptom free and shows no evidence of disease eighteen months postoperatively. Although only 47 years of age, she and her husband have accepted the situation philosophically as the only alternative to an otherwise hopeless state (Fig. 4).

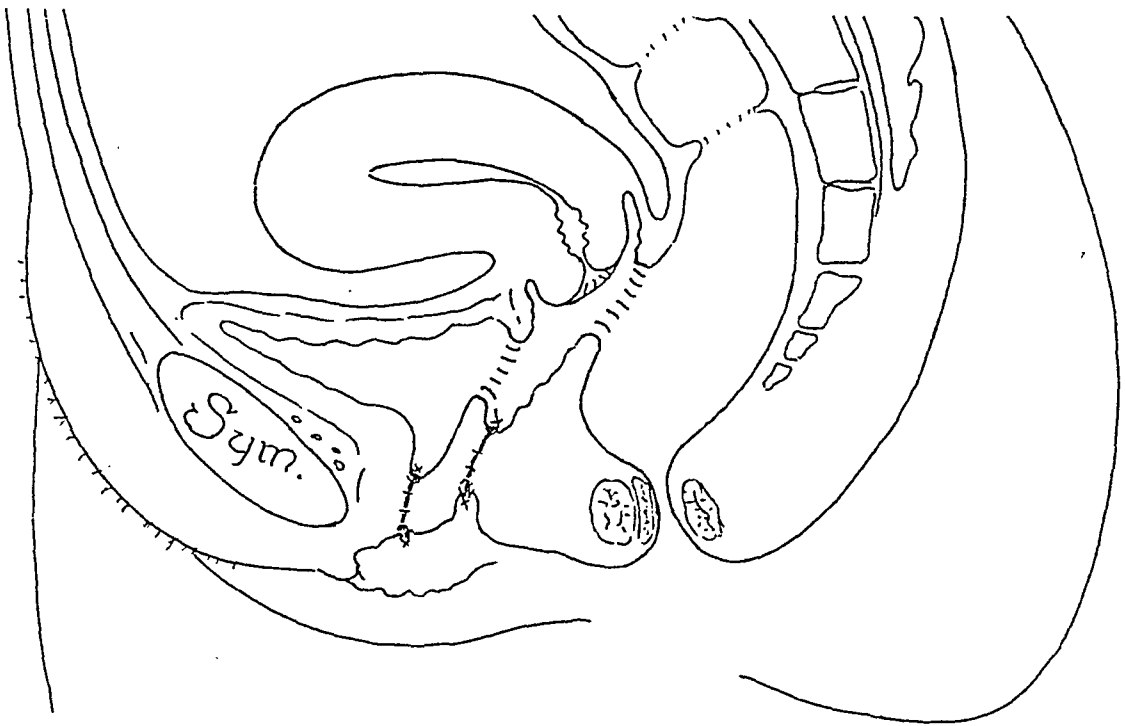


Fig. 6.

One patient whose vesicorectovaginal fistula was treated by vaginectomy was found to have a complete urethral incontinence after the operation. She had stress incontinence previous to her cancer therapy and the worsening was partly due to the resulting genital atrophy and perhaps in part to the vaginectomy being carried too low so that the urethra was pulled open thereby. She was treated by excision of the lower portion of the urethra and closure of the raw surfaces. A small sinus resulted which soon closed spontaneously, all urine being voided per rectum (Fig. 6).

Not all patients are so fortunate. Loss of the trigone along with cicatrization and retraction markedly alters the relationship of the ureteral orifices and angulates the ureter and this makes dilatation quite difficult and sometimes impossible. A patient with a large fistula of the entire trigone was treated successfully with vaginectomy and did well for seven months when it was found that both of the ureteral orifices were again badly obstructed and azotemia was present. The function of the right kidney was completely gone and marked hydronephrosis and hydroureter were present on the left. Attempted dilatation of the stricture from above, i.e., through pelvic ureterotomy, failed of permanence and the patient spent her remaining days with a cutaneous ureterostomy.



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## Discussion

DR. WAVERLY R. PAYNE, Newport News, Va.—Dr. Williams has presented this subject in a most comprehensive manner, and I found many points of interest. I fully agree with the principles set forth, and would like to emphasize the importance of considering all such cases as joint problems of the gynecologist and the urologist. The avoidance of tension on the suture line, both of the bladder and the vagina, is absolutely essential to success. The idea of producing a temporary descensus in certain cases seems logical, and I would like to ask if he has considered an external perineal band, such as a metal catheter holder, for attachment of the traction sutures. It is my impression that some extensive fistulas, especially those encroaching upon the ureters, can better be repaired by the intravesical approach from above. The crux of this problem is the individualization of cases from the standpoint of etiology, location, and complicating conditions.

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Pascual, Garcia Romeu Y Rivas: The Value and Interpretation of the Rh Factor in Obstetrics in Cuba, *Rev. cubana de obstet. y ginec.* 9: 123-131, Dec., 1947.

The authors classify the major blood groupings and Rh factor determinations in pregnancy and in different racial mixtures. Among 475 patients of the white race they found 220 (46.3 per cent) group O; 199 (41.8 per cent) group A; 44 (9.0 per cent) group B; and 12 cases (2.9 per cent) of group AB. Among 291 cases of mestizo women (hybrids of white and American Indian blood) were 135 cases (46.4 per cent) of group O cases; 105 (36.0 per cent) group A cases; 44 (15.1 per cent) group B; and 7 cases (2.5 per cent) group AB.

Among 307 women of the Negro race were 153 (49.8 per cent) group O blood; 72 cases (23.4 per cent) group A; 68 cases (22.2 per cent) of group B; and 14 cases (4.6 per cent) of group AB. One hundred males of the yellow race showed 42 instances (42.0 per cent) of group O; 30 cases (30 per cent) group A; 26 cases (26 per cent) group B; and 2 cases (2 per cent) of group AB.

The Rh factor was determined in 1,184 cases distributed as follows by race: (1) white race with 424 cases (87 per cent) Rh positive and 63 cases (13 per cent) Rh negative; (2) mestizos (hybrid white and American Indian) 266 (92 per cent) were Rh positive and only 8 per cent (23 cases) were Rh negative; (3) among 306 of the Negro race, 95 per cent (281) were Rh positive and 5 per cent (15 cases) were Rh negative; while (4) 100 per cent of the 102 Chinese were Rh positive.

Because of these racial variations the authors stress the importance of Rh and major blood group determinations in obstetrical practice in Cuba.

CLAIR E. FOLSOME.

## THE USE OF PYRIDOXINE AND SUPRARENAL CORTEX COMBINED IN THE TREATMENT OF THE NAUSEA AND VOMITING OF PREGNANCY\*

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WITH the exception of abortion, probably nothing which occurs in the first trimester of pregnancy causes more general discomfort to the patient, nor more worry and effort on the part of the obstetrician in his endeavor to correct it, than nausea and vomiting. We are all fully aware of the marked improvement which has been made in the treatment of this condition in the relatively recent years, especially in the true pernicious vomiting, yet certainly, if the experience of others is similar to that of the writer, the control of the milder cases—from a mere uncomfortable morning nausea up to a moderate degree of vomiting—still leaves much to be desired.

It is needless to go into a review of the many varied and some even bizarre treatments now in usage, which approach the problem from practically as many angles as there are measures employed, and with as many variations. Suffice it to say that nearly everything imaginable has been attempted, from therapy based on pure superstition at one end of the treatment scale up to those measures which have as nearly a true physiological background as is possible in any condition where the exact etiological factor is still unknown. As evidence of the multiplicity of drugs employed, it is of interest to note that the Physicians Desk Reference for 1949<sup>1</sup> lists, under the heading of "Nausea—Pregnancy," some twenty-three preparations available through varied drug houses, and its list of such houses and preparations is not complete.

It is the purpose of this paper to present simply and briefly the results obtained with the use of pyridoxine and suprarenal cortex combined in the treatment of sixty-two cases of nausea and/or vomiting of pregnancy, without any attempt whatever to establish a comparative evaluation with other methods. Neither is this looked upon as a panacea, which the author feels will probably never be reached until an approach can be made based on the knowledge of the exact etiology, but merely as another weapon in our armamentarium, which seems to have some advantages over, and fewer disadvantages than, some of the other therapy now in vogue.

Before outlining the method of administration, it might be worth while to refresh our memories briefly on the pharmacological properties and physiological actions of the drugs concerned. Vitamin B<sub>6</sub>, or pyridoxine is, according to Goodman and Gilman,<sup>2</sup> "... one of the components of the vitamin B complex known to be essential in animal nutrition. Although a discrete vitamin B<sub>6</sub> defi-

\*Read at the annual meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Va., Feb. 10 to 12, 1949.

ciency has not been described in man, evidence has been obtained from the treatment of multiple deficiency states that some of the symptoms accompanying the ingestion of inadequate diets may be the result of a B<sub>6</sub> deficiency. . . . It is a pyridine derivative. . . . There is evidence that the physiological function of vitamin B<sub>6</sub> is linked with the utilization of unsaturated fatty acids. From a pharmacological point of view, pyridoxine is rather inert. . . . In man, intramuscular injections cause pain, but the oral or intravenous administration of 100 to 200 mgm. is without untoward effect. . . ."

The same authorities, Goodman and Gilman,<sup>2</sup> say the following about the adrenal cortical hormones:

"The chemistry of the active principle of the adrenal cortex resembles that of the sex hormones in several ways. There are numerous chemically related compounds, possibly a score or more, obtainable from the cortical tissue, most of which possess some degree of physiological activity, just as there are chemically related estrogens and androgens. There is a marked similarity in the chemical structure of the adrenal cortical and sex hormones, especially the androgens. Also, the esterification of adrenal cortical hormones increases their potency and duration of action. . . . The close relationship of the cortical hormones to testosterone is evident."

The physiological activities of these hormones are not listed per se, but the authors approach this subject from the angle of the effects of hypofunction or ablation of the gland, and state three such effects: "(1) A marked abnormality in the metabolism of sodium, resulting in a negative balance of this ion, a fall in the total electrolyte content of the extracellular fluid and a resulting shift in the distribution of body fluids. (2) There is an abrupt increase in the concentration of potassium in the extracellular fluids associated with a decreased renal excretion of this ion. (3) Carbohydrate metabolism is seriously altered as is evidenced by a diminished concentration of glucose in the blood and a greatly reduced glycogen content of liver and muscle." They state that all these ill effects can be corrected by the injection of the hormones concerned.

From these facts the rationale and physiological basis of the treatment can be established. If, as is stated above, the ingestion of inadequate diets may be the result of a vitamin B<sub>6</sub> deficiency, then it seems logical to presume that, in the presence of vomiting, an oversupply of this same vitamin might reasonably be effective in changing the metabolic picture so that food could be taken and retained. In like manner, the addition of the adrenal cortical hormones may, as its greatest part in this particular condition, aid materially in correcting the upset carbohydrate metabolism by restoring the proper glucose concentration in the blood. It may also, from its close chemical similarity to the sex hormones, play some part in correcting any abnormal reaction which may have occurred in them.

It should be mentioned that in addition to the exact therapy, such generally accepted supportive measures as bed rest, mild sedation when tolerated orally, repeated small feedings alternating liquids and solids, etc., were used in all cases. Nor were the injections used when the above measures produced the desired results.

The treatment consisted of the intramuscular injection of 25 mg. of pyridoxine combined with 0.5 c.c. of suprarenal cortex (Armour) or adrenal cortex extract (Upjohn). The patient was given two injections at an approximate twenty-four hour interval, regardless of the response to the first injection. Further injections were given as required, the patient being instructed to return at the first reappearance of nausea, and not to delay until vomiting occurred. If there was no improvement following the first two administrations, experience proved that further similar treatments were, in most cases, unsuccessful, and

in those cases hospitalization and the use of intravenous glucose and saline gave prompt relief. This will be discussed further in the consideration of the cases listed as failures.

It may be asked why a second dosage was given to those patients who showed favorable reaction to, and cessation of symptoms from the initial injection. One injection only was given at the time the treatment was first used, but in the great majority of those so treated, symptoms returned to some degree within three to five days. Because of this, the two-treatment routine was adopted, and the results have since been much more favorable, showing a much higher percentage of cures with fewer total injections.

As mentioned above, the series consisted of 62 patients; 30 primiparas and 32 multiparas. Of the primiparas, nine were treated by the one-injection method. Of these, three obtained complete relief, five were cured following a second injection, and one required a third treatment, five days after the second had been given.

The remaining 21 primiparas received the two-injection method, with complete cure in eleven, and improvement in all the others, two of whom had such slight morning nausea remaining that they felt it unnecessary to receive further treatment, one of whom aborted, three of whom had a third, and four a fourth injection before complete cessation of symptoms. Those who received more than two treatments got the third three to five days after the second, and in all cases where a fourth injection was given, it was five days after the third. With a few exceptions, the number of injections needed was in direct ratio to the severity of the symptoms when the treatment was first started.

Thus it will be seen that, in the primiparas, cure was obtained in all cases save that of the one patient who aborted, and she was greatly improved following her second injection. It is likewise apparent that cure was accomplished by one injection in one-third of the cases so treated, three of nine, and in roughly half of those given the two-injection treatment, eleven of twenty-one, with only the initial treatment.

In the case of the multiparas, the picture was somewhat, but not tremendously different. There were twelve treated by the one-injection method with three cures; one required two, three had three, three received four, one needed five, and one had to have ten injections to obtain complete relief. Of the remaining twenty cases treated by the two-injection method, ten obtained complete relief with the two initial treatments, four required three, one received four, one had five, and one needed nine injections before being cured. There were three failures.

So it will be seen, as in the case of the primiparas, that the percentage of cures with one injection was lower than with the initial two-injection routine. There is a moderate variation between the primiparas and multiparas cured by one injection, 33 per cent in the former and 25 per cent in the latter, but the cures with two injections are almost exactly the same, eleven of twenty-one, and ten of twenty. Also, there was definite improvement in all cases except those listed as failures. In both the one- and two-injection series, there was one cure in which more than five injections were necessary.

Let us consider these two patients who needed ten and nine treatments, respectively, before complete relief was obtained. The first was extremely nervous, had been treated for nervous breakdown approximately eighteen months prior to this pregnancy, and had been advised not to attempt any more pregnancies, and told she would probably go crazy if she did become pregnant again. The other eventually was delivered by cesarean section because of premature separation of the placenta at about seven and one-half months' gestation, and at operation a bicornuate uterus was found, with the pregnancy in the small cornu.

The failures were as follows:

1. A gravida iii who had an associated true ptalism of pregnancy.
2. A gravida ii whose first baby was ten years of age, and who, meanwhile, had two major abdominal operations, one being an oophorectomy because of cystic ovary, and who was treated for acute cholecystitis six months prior to her pregnancy.
3. A gravida v who was an habitual aborter and who aborted spontaneously in her fourth month.

These patients, as previously mentioned, all responded to glucose therapy, the first two eventually delivering normal babies at term.

It would therefore seem that this method of treatment has been successful in all cases uncomplicated by either systemic or other obstetric abnormalities, and, likewise, save in such cases, the cure has been obtained with a maximum of five administrations of the combined drugs.

One tends to recall most vividly those things which are most tragic or dramatic. Since the failures have been considered, may I briefly outline the case in which the most dramatic favorable result was obtained.

The patient was a primipara, aged 20 years, who was approximately eight weeks pregnant when first seen. She had been vomiting severely for two weeks, had lost 14 pounds, and was in such weakened condition that she had to be practically carried into the office. She was given the initial injection, and, because she lived at a distance of sixty miles, was advised to remain at a local hotel overnight, and to return the following day. She did not return, and it was presumed she had returned to her family physician at home. However, twelve days later she reappeared and was not recognized. She felt fine, had gained back twelve pounds of her previously lost weight, and had had complete relief of symptoms within twelve hours after the injection was given. She had no later difficulties.

The results of the one- and two-injection series are shown graphically in Tables I and II, respectively, and of the total series in Table III.

TABLE I. ONE-INJECTION METHOD, 21 CASES

	PRIMIPARAS	MULTIPARAS
Cured, 1 injection	3	3
Cured, 2 injections	5	1
Cured, 3 injections	1	3
Cured, 4 injections	0	3
Cured, 5 injections	0	1
Cured, more than 5 injections	0	1
Failures	0	0
Total	9	12

TABLE II. TWO-INJECTION METHOD, 41 CASES

	PRIMIPARAS	MULTIPARAS
Improved, took only 2 injections	3	0
Cured, 2 injections	11	10
Cured, 3 injections	3	4
Cured, 4 injections	4	1
Cured, 5 injections	0	1
Cured, more than 5 injections	0	1
Failures	0	3
Total	21	20

# PENICILLIN THERAPY IN THE OBSTETRICAL PATIENT

## A Study of Its Effect on the Bacterial Flora of the Postpartum Uterus

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THE purpose of this paper is to present the results of an investigation of the effect of penicillin on the bacterial flora of the postpartum uterus. Harris and Brown<sup>1</sup> showed that the gravid uterus is ordinarily sterile before the 6th hour of labor but is usually not sterile after that time; and various other investigators have established the fact that the postpartum uterus almost always contains numerous bacteria.<sup>2, 3</sup> This study was undertaken in order to determine what effect, if any, penicillin administration may have on such bacteria; how morbidity and complications may be affected; and what would be the possibility of complete sterilization of the uterine cavity by this means in the first few days post partum.

### Methods

Cultures were obtained from the uterine cavities of 86 postpartum patients, 54 of whom received varying amounts of penicillin and 32 of whom were untreated. The material was obtained by a new technique which has been described elsewhere,<sup>4</sup> and which, we believe, greatly reduces contamination by organisms from the vagina and cervix. This was substantiated by the fact that a number of uterine cultures, not included in our series, which were taken with a Little tube<sup>5</sup> from patients receiving intramuscular penicillin, all showed bacterial contaminants; while, in a similar group of patients on the same therapy, culture material taken by the new technique was often sterile (Table III). Therefore, we think that the organisms isolated in the control series of untreated patients represents the true bacterial flora of the postpartum uterus, and that the results of the cultures taken from patients receiving penicillin represent a true picture of the effect of penicillin on such organisms in the postpartum uterus.

The material collected from the uterine cavity was immediately inoculated into Brewer's thioglycollate medium<sup>6</sup> and sent to the laboratory. Here 0.1 c.c. of a 4 per cent sterile solution of clarase (final concentration 0.25 per cent) was added to the culture to neutralize any penicillin which might be present in the inoculum, and 2 c.c. of sterile ascitic fluid (final concentration 20 per cent) to enhance the growth of pleuropneumonia-like organisms. Methods followed for the isolation and identification of the various bacteria were those outlined in Schaub and Foley's "Diagnostic Bacteriology," third edition.<sup>7</sup> The penicillin sensitivity of all organisms isolated was determined by the paper disc technique described by Bondi and associates,<sup>8</sup> and the results are given in Table II.

The organisms isolated from the uterine cultures were of the species generally accepted as representing the normal flora of the postpartum uterus with but one exception. A review of the literature has shown that this is the first

per cent of those having nausea and vomiting had had dysmenorrhea previously. In his conclusion he stated, "A review of the number of cases obtained in each group in comparison with the number that would be expected on a chance basis alone leads one to the conclusion that there is some common factor between dysmenorrhea and nausea and vomiting of pregnancy that could very well be psychogenic, since there is no obvious common anatomic nor physiologic relationship known."

For years, the Smiths have been working on the endocrinology of menstruation and ovulation. More recently they have found a high fetal salvage using stilbestrol in pregnant diabetics, and in the November, 1948, issue of the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY*, O. Watkins Smith told of the use of diethylstilbestrol in the prevention and treatment of complications of pregnancy in 632 cases. Her cases were observed for threatened abortion, the complications of late pregnancy, and premature delivery. She concluded, "Considering the past obstetric histories of these patients, the course and outcome on stilbestrol gave good indication that the administration of this drug as a preventive measure may be expected to reduce the incidence of those complications of later pregnancy associated with a premature deficiency of the placental steroid hormones, estrogen and progesterone."

My associate, Dr. Bertling, revised his thinking on the psychic aspects of dysmenorrhea and nausea and vomiting of pregnancy and we decided that if nausea and vomiting of pregnancy are a toxemia of early pregnancy it might well be due to a deficiency of the placental steroid hormones, since in most instances it "spontaneously" clears up around the fourth or fifth month, the time the placenta is taking over almost the entire production of the steroids. Thus stilbestrol should be the treatment and we now have been using it since October, 1948, in nausea and vomiting. This deficiency of placental steroid hormones may probably be the exact etiology Dr. Dorsey says has not been found. In our stilbestrol series, we used no supportive measure, but stilbestrol alone.

DR. C. J. COLLINS, Orlando, Fla.—I know of no other condition in which it is more difficult to evaluate the value of a specific treatment than in the nausea and vomiting of pregnancy. We are all aware of the tremendous psychic effect of any treatment in this disorder and this factor is difficult to eliminate when we attempt to arrive at accurate and logical conclusions. I was supplied with pyridoxene for experimental purposes when it was first introduced and tried it on a series of cases with no startling results. I concluded that it was of no more value than thiamine chloride and subsequently administered both of them in 50 mg. doses with, as I thought, better results. I also used adrenal cortex some years ago, giving it often in 1 c.c. doses before each meal. I was not impressed with its value and gave it up. Dr. Dorsey's results with their combined use has certainly been better than I ever obtained from either one alone. This suggests that there may be some synergistic action between them. He has offered a physiologic basis for their use and it appears that in this respect a better case can be made for adrenal cortex. His doses have been small and it is a little difficult to understand how two administrations could correct a disturbed metabolic state sufficiently to cure the patient. However, his results have been so good, one-third of all cases cured with one injection and one-half with two injections, with a total cure of 95 per cent, that his presentation cannot be brushed aside as just another treatment, but must be considered seriously as a scientific approach to a most troublesome condition. He has had three failures in sixty-two cases or about one in twenty. I doubt that many of us have ever found it necessary to hospitalize more patients than that for treatment no matter what his favorite routine may be. The main advantage of his treatment seems to be its prompt beneficial effect and that is what the patient wants, prompt relief. Until our understanding of the etiology of the nausea and vomiting of pregnancy has increased to the point that we can develop a specific treatment, it is our duty to employ that one which offers the greatest promise of relief.

TABLE III. TOTAL CASES, 62

	PRIMIPARAS	MULTIPARAS	TOTAL
Cured	27	29	56
Improved	3	0	3
Failures	0	3	3
Total	30	32	62

### Summary

1. A series of 62 cases of nausea and/or vomiting of pregnancy treated by the use of pyridoxine and suprarenal cortex combined is presented.
2. The chemistry and physiology of the drugs are briefly reviewed.
3. There were 56 complete cures, with such marked improvement in two and possibly three others that they may also be reasonably considered as cures, making a total of 58 or 59, with a percentage cure of 93.5 per cent or 95.1 per cent.
4. In all cases uncomplicated by coexisting systemic disease or other complication of pregnancy, cure was obtained with not more than five injections.
5. The most effective method of administration is apparently to give two injections at a twenty-four hour interval, these being supplemented by further treatment if and when symptoms reappear.

### Conclusion

From the ease of administration, lack of discomfort to and beneficial effects obtained by the patient, it is felt that the injection of pyridoxine and suprarenal cortex combined is a worthy addition to the measures employed in the treatment of the nausea and/or vomiting of pregnancy.

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### Discussion

DR. JOHN B. DUNCAN, Atlanta, Ga.—I think from my own experience that patients who really want their babies, in about 98 per cent of the cases, are most cooperative. I can recall only two cases in my practice where it was necessary to do an abortion on account of continued vomiting. These two cases were before vitamin B<sub>6</sub> and adrenal cortex were used, although both patients were admitted to the hospital and given Sodium Amytal and intravenous glucose, with a small daily enema, routine rest in bed, several small meals, and a mild sedative. In spite of all this I had to do a therapeutic abortion. One patient, I might add, had a large cystic ovary on the right side which I removed later on and, subsequently, she became pregnant and I delivered a baby without any trouble.

As Dr. Dorsey has stated, if there is any pathology in the pelvis, it is much more difficult to control the vomiting. For the past several years, I have used vitamin B<sub>6</sub> every other day, in a great many cases, usually for five or six doses, and have had excellent results from about 65 to 75 per cent of the cases, but I am very happy to know that there is another drug available which increases the efficiency and makes the early months so much more pleasant for the patients who are suffering from this extreme nausea.

DR. JOHN BURWELL, Greensboro, N. C.—In the October, 1948, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, Dr. M. H. Bertling showed the very high correlation of nausea and vomiting of pregnancy with dysmenorrhea. Sixty-eight and one-half



TABLE I. BLOOD LOSS IN CUBIC CENTIMETERS

BLOOD LOSS IN C.C.	NO. CASES	PER CENT
0.99	572	68.0
100-199	205	24.4
200-299	47	5.6
300 or more	17	2.0
Total	841	100.0

I have no accurate records as to the amount of bleeding in cases before I adopted the use of caudal analgesia, but in common with all observers I have been impressed with the greatly decreased bleeding as compared with that when other methods of anesthesia were used.

In all cases all blood was collected in the sterile placenta basin during the third stage. The patients were also observed carefully for one hour after the third stage and any additional bleeding estimated. I have been particularly impressed with the tone of the uterine muscle after the end of the third stage. Very few patients required any massage to maintain a firm hard fundus.

It has been argued that, since placenta previa has been considered a contraindication for the use of caudal or spinal analgesia, necessarily a group of cases with excessive bleeding are excluded from such a report as this. This is, perhaps, a just criticism. However, Thorp<sup>6</sup> used this method in twelve cases of marginal placenta previa with a blood loss of less than 125 c.c. in every case.

I have had several cases in which a marginal implantation of the placenta was not diagnosed until after caudal analgesia had been administered and labor was in progress. In none of these was there excessive bleeding. It is reasonable to suppose that there may have been other cases of low or marginal implantation in which the true condition was not recognized. In common with other observers I have noticed that the uterine tone is increased to the point that Pituitrin should not be used at the end of the second stage. I had previously used 1 c.c. of Pitocin or Pituitrin but soon noted that with caudal there is a danger of a trapped placenta with this routine. As a result, the procedure has been changed to omit any oxytocic until after the end of the third stage. It is immediately apparent, after seeing only a few cases, that uterine tone is better and the bleeding markedly less than most of us have been accustomed to seeing.

What of pain relief? This is the primary reason for using caudal analgesia. Here again my figures rather closely approximate those of others. The results were classed as good, fair, and failure. In the first group there was complete relief of pain. In the second group the greater portion of pain was abolished but the patient had variable amount of pain such as slight pain in either groin or moderate pain at the peak of contraction. In those classed as failures there was little or no relief of pain. As shown in Table II, 759, or 90.2 per cent of cases, had complete relief, 59, or 7 per cent, were classed as fair, and there were 23 failures, 2.8 per cent of all cases.

TABLE II. RELIEF OF PAIN IN CONTINUOUS CAUDAL ANESTHETIC

	NO. CASES	PER CENT
Complete relief	759	90.2
Partial relief	59	7.0
Failures	23	2.8

It should also be noted that my experience more or less parallels that of Ellis and Sheffrey.<sup>3</sup> During the first 100 cases the failures were more common.

# CONTINUOUS CAUDAL ANALGESIA IN OBSTETRICS\*

## Experience in 841 Cases in Private Practice

ALBERT J. KELLEY, M.D., SAVANNAH, GA.

THIS report is somewhat unique in that it covers a rather large series of cases, in all of which one man acted as both anesthetist and obstetrician. From February, 1944, to October, 1948, there were 841 vaginal deliveries under continuous caudal analgesia in the author's private practice. Savannah has no hospital connected with a medical school and there are no well-organized resident and intern staffs. Outside anesthetists are not always available when needed and under these conditions the obstetrician must rely on himself for a satisfactory method of pain relief. Many of the members of this society practice under similar conditions and hence this report should be of interest.

In the past few years there has been a notable increase in the use of various methods to control pain in childbirth. Less and less do we hear that women are "supposed to feel their pains," that "the pains of childbirth are soon forgotten," or that "suffering in childbirth increases a mother's love for her child."

Also during the past few years there has been a decided decrease in the maternal death rate. Due to improved methods, better education of the patient and physician, and due to improved measures of combating infection, the most notable decrease has been in deaths from eclampsia and from infection. Consequently recent reports have shown that bleeding has become relatively more important as a cause of maternal deaths.

Parker and Allison<sup>5</sup> in a report read before this society last year have shown that in Greenville, S. C., hemorrhage accounted for six out of thirty-six deaths in 6,413 deliveries from 1938 to 1942. From 1943 to 1947, hemorrhage accounted for eight out of twenty-seven deaths in 13,676 deliveries.

Several reports<sup>1, 2, 3, 4</sup> have indicated that bleeding is definitely less in cases where some form of nerve block is used as the anesthetic agent. This is logical because any properly administered nerve block does not interfere in any way with normal uterine contractions. Any sedative or general anesthetic must, however slightly, decrease the tone of the uterine muscle and the force of the contractions.

In 841 vaginal deliveries conducted under continuous caudal analgesia there was an average blood loss of 109.5 c.c. This compares very closely with the experience of Vaux and Mitchell<sup>1</sup> in 1,000 cases and with the study of twenty-eight months' experience at Philadelphia Lying-In Hospital as reported by statisticians Collins, Phillips, and Oliver.<sup>4</sup>

Table I shows that 68 per cent of the patients had a blood loss of less than 100 c.c., while only 17, or 2 per cent, had blood loss of over 300 c.c. In this series there was no patient with a blood loss of more than 500 c.c. and only 2 cases reached this figure. This distribution is comparable to the figures of Vaux and Mitchell and, as their review of the literature showed, is far less than in most other published series.

\*Read at the annual meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Va., Feb. 10 to 12, 1949.

In a report last year<sup>7</sup> I cited two cases of shock produced by caudal in cesarean sections. In these cases the difficulty was undoubtedly due to too rapid and too forceful injection of the drug.

The present report includes only cases of vaginal delivery. In this series there have been no cases of shock, no serious drop in blood pressure, and no serious sequelae. There have been three cases of a mild infection at the site of injection. None of these were serious but in one patient, a diabetic, there was a rather widespread low-grade cellulitis, which did not clear completely for two months.

Some mention should be made also of saddle-block or controlled-level spinal anesthesia. Although I have not included them in this report I have used this technique a good many times, particularly in the past year.

The results with this method are very comparable to those with caudal analgesia. There is good pain relief, bleeding is decreased, and the patient is in good condition afterward. Also, as in caudal, it is very striking to note the lack of narcotization of the babies.

Technically, saddle-block analgesia is easier to give. Hesseltime<sup>9</sup> states that at Chicago Lying-in Hospital they prefer it to caudal because all medical students know how to do a spinal tap; therefore, as interns and residents, they require less teaching to give a spinal anesthetic than is the case with caudal.

One must, however, remember that with saddle-block the entire dose must be estimated in advance. It varies with the height and weight of the patient. In continuous caudal the dose is given fractionally and is therefore easier to estimate accurately.

Duration of saddle-block anesthesia varies from one to three hours. I personally do not like the idea of repeated spinal punctures during a labor. This would seem definitely to increase the hazard of infection but those more experienced than I report no difficulty. Saddle-block anesthesia gives effective pain relief in two to three minutes whereas in caudal from ten to twenty minutes are required to establish complete relief.

I have, therefore, recently used saddle-block in those cases where pains are frequent and tumultuous and where it is apparent that labor will be completed within sixty to ninety minutes. Also, I find saddle-block anesthesia invaluable in cases where the sacral hiatus is not palpable or where caudal is failing to give complete relief of pain.

Aside from these factors I find little to choose between the two methods. I would like to add one word of caution. Do not be fooled by the apparently easier technique of saddle-block. There is many a patient who has been prodded in the back for fifteen to twenty minutes in an attempt to find spinal fluid and in whom the insertion of a needle into the sacrum would be simplicity itself.

### Conclusions

1. Eight hundred forty-one cases of vaginal delivery under continuous caudal analgesia have been eminently satisfactory with administration of analgesia and delivery done by one person.

2. In confirmation of reports by other authors, bleeding is found to be minimized, averaging 109.5 c.c. per patient.

3. Pain was completely relieved in 90.2 per cent and partially relieved in 7 per cent of cases.

4. Forceps were used in 87.6 per cent of primiparas and 44.2 per cent of multiparas.

5. A brief comparison is made between caudal and saddle-block analgesia.

With increasing experience in the method, the results have improved. This is partly due to better technical skill in properly placing the needle, better selection of cases, eliminating those cases where it is impossible properly to palpate the sacral hiatus. Also with experience one is enabled to judge better the hysterical or psychologically unstable individuals. These patients, even though relieved of pain, find many other complaints such as nausea. They complain bitterly of numbness of the legs and are totally uncooperative. They are doubtless better off if they are asleep during delivery. Several such individuals had to be classed as only fair in judging results in this series.

Having pointed out that in continuous caudal we have a method highly successful in the relief of the pain of labor and one which definitely is accompanied by less bleeding, it is only fair to note some of the dangers and disadvantages.

Technically, caudal is perhaps more difficult than other forms of anesthesia. It is a technique, however, that can easily be learned by any obstetrician in a comparatively short time. Therefore the objection of technical difficulty is only a relative one.

The patient must be watched in a somewhat different manner than other patients. Because the method is not in widespread use the average student nurse is not trained to watch these patients. The average supervisor of the delivery room has not been trained and hence is distrustful of the method. But it is relatively easy to train any competent obstetrical nurse to care properly for these patients.

It has been argued that caudal analgesia necessitates the more frequent use of forceps. I list this as a disadvantage because most of us were taught the traditional abhorrence of forceps. However, more and more obstetricians in recent years have advocated episiotomy and forceps on all primiparas as soon as the head reaches the perineum. I personally believe that one or two hours of second stage pains accompanied by tremendous voluntary exertion by the mother is prone to produce maternal exhaustion, excessive perineal damage, and increased frequency of cranial injuries.

Table III shows the type of delivery of 848 infants delivered to 841 mothers in this series. Forceps were used in 87.6 per cent of primiparas and 44.1 per cent of multiparas.

TABLE III. TYPE OF DELIVERY IN 848 BIRTHS TO 841 MOTHERS

TYPE OF DELIVERY	PRIMIPARAS		MULTIPARAS	
	NO.	PER CENT	NO.	PER CENT
Spontaneous cephalic	44	9.8	212	52.6
Forceps	389	87.6	178	44.2
Spontaneous breech	1	0.2	11	2.7
Breech extraction	11*	2.4	2	0.5
Total	445	100.0	403	100.0

\*Forceps were used on the aftercoming head in only one case.

It is of interest that in twenty-five breech deliveries, it was necessary in only one case to use forceps on the aftercoming head. This attests to the fact that with the perineum well anesthetized and relaxed, delivery of the aftercoming head is relatively rapid and easy.

Much criticism has been levelled at caudal analgesia because of its potential dangers. Some of the criticism has been just and some unjust. Caudal does have its hazards just as does any method of anesthesia or analgesia. It is not within the scope of this paper to dwell on this aspect. I will, however, state that most of the untoward results in caudal analgesia have occurred as a result of ignoring the proper safeguards and precautions as originally set forth by Hingson.<sup>8</sup>

# CONTINUOUS SPINAL ANESTHESIA IN THE TREATMENT OF SEVERE PRE-ECLAMPSIA AND ECLAMPSIA\*

## A Preliminary Report of a Study of 24 Cases

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AND E. C. SCHELIN, M.D., RICHMOND, VA.

(From The Medical College of Virginia Hospitals)

PRIOR to 1947 the treatment of patients with severe toxemias of pregnancy in The Medical College of Virginia Hospitals had remained about the same for fifteen years. This treatment was outlined in the *Southern Medical Journal* in 1937<sup>1</sup> by one of the authors and again by the same author in the *Virginia Medical Monthly* in 1939.<sup>2</sup>

During the year 1947 in The Medical College of Virginia Hospitals several cases of severe pre-eclampsia and eclampsia were treated with regional nerve block anesthesia. In 1943, Hingson and Edwards<sup>3</sup> reported the use of caudal anesthesia in the management of twelve patients with severe toxemia of pregnancy. These authors described the following observations:

1. There was a slow progressive blood pressure fall, frequently amounting to 100 mm. of mercury within one hour. Associated with this reduction in vascular tension there was a warming, blushing, and drying of the lower extremities similar to that following bilateral lumbar sympathectomy.

2. There was an increase in the urinary output with a reduction in the concentration of the urine. We explain this phenomenon by the suggestion that the sympathetic nerve supply to the kidneys was blocked, with the corresponding maximum dilatation of the glomerulus and afferent arterioles.

3. Convulsions were controlled without resort to other forms of sedation.

4. The mental cloudiness of these patients cleared remarkably, they became more cooperative and three of them were able to take fluids and small servings of food.

5. There was no appreciable change in the heart rate of the fetus, and all of them were delivered without mortality or unusual postpartum morbidity.

At the Medical College of Virginia Hospitals difficulty has been experienced with the use of caudal anesthesia. With the patient in an unconscious state it was difficult to determine the proper time for injections of maintenance doses of the anesthetic agent. Once the level dropped too low, it was almost impossible to re-establish the required level of anesthesia. After a duration of twelve to fifteen hours the required level of anesthesia could not be maintained. Since most of our cases required anesthesia over a longer period of time, we changed to continuous spinal anesthesia.

\*Read at the annual meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Va., Feb. 10 to 12, 1949.

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4 TAYLOR STREET, EAST

## Discussion

DR. W. C. WINN, Richmond, Va.—At the Medical College of Virginia Hospital, caudal analgesia has been used with very gratifying results in patients with toxemia, cardiac disease, and in other cases where it was preferable to avoid inhalation anesthesia.

To administer caudal anesthesia safely and successfully, it should be used only in well-equipped hospitals, and administered by specially trained and competent individuals. The careful selection of patients for its use is extremely important.

When there is a definite indication or need for its use, it is most helpful and a valuable addition to our armamentarium. The obstetrician who has a large practice or heavy teaching responsibilities, however, is not able to remain with the patient constantly during labor. Employing a physician anesthetist for the average uncomplicated labor and delivery would be an additional financial burden for the patient. For these reasons, in my opinion, its use in the average normal labor and delivery is not very practical.

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Fried, Paul H.: *The Two Hour Pregnancy Test, Based on Rat Ovary Hyperemia*, West. J. Surg., page 552, Oct., 1948.

Hyperemia of the rat ovary occurs shortly after the animal is injected with chorionic gonadotropin. The reaction may occur within 10 minutes and is maximum at six hours. This lends itself to a quick, inexpensive test for pregnancy, the accuracy of which may be better than 95 per cent. The two-hour rat test was performed on 516 urine specimens and the reaction compared to that of the Friedman test performed on the same specimens. There were sixteen errors in pregnant and nonpregnant cases for an accuracy of 96.8 per cent. In 200 cases of normal intrauterine pregnancies there were eleven errors for an accuracy of 94.5 per cent. In 100 cases of disturbed pregnancies such as ectopic pregnancy, threatened, and incomplete abortions, where a rapid and accurate test for pregnancy is of the greatest importance, the two-hour test gave a percentage accuracy comparable to the Friedman test. The percentage of error in both was sufficiently high to make dubious the clinical value of either. The greatest incidence of error in the two-hour rat test as compared with the Friedman test is the false negatives.

The technique is described in some detail and is relatively simple. The chief difficulty is found in the comparison of the color changes secondary to hyperemia with the standard color charts. Absence of a sharp, positive endpoint makes necessary considerable experience with the test before accuracy of interpretation is obtained.

WILLIAM BICKERS.

Table IV shows the incidence in reference to parity.

TABLE IV. INCIDENCE IN REFERENCE TO PARITY

PARITY	NO. OF CASES	PER CENT
Primiparas	19	79.1
Multiparas	5	20.9
Total	24	100.0

Table V shows the average, high, and low blood pressures at the time of admission to the hospital. The table clearly indicates the severity of both the pre-eclampsia and eclampsia.

TABLE V. BLOOD PRESSURE AT THE TIME OF ADMISSION

	HIGH	LOW	AVERAGE
Pre-eclampsia	210/140	175/95	181/116
Eclampsia	250/130	135/80	175/106

Table VI shows the incidence in reference to the convulsive seizures that occurred prior to admission to the hospital and also those that occurred after admission but before treatment with spinal anesthesia was started.

TABLE VI. CONVULSIVE SEIZURES

NO. OF CASES	CONVULSIONS PRIOR TO ADM.	CONVULSIONS AFTER ADM. PRIOR TO SPINAL	AVERAGE NUMBER CONVULSIONS PER PATIENT
12	78	24	8.5

Table VII shows the incidence of patients as related to antepartum, intrapartum, and postpartum groups.

TABLE VII. TYPE OF ECLAMPSIA

	ANTEPARTUM	INTRAPARTUM	POSTPARTUM	NO. BABIES
Eclampsia	8	2	2	11

Two of the patients with eclampsia were admitted to the hospital after delivery. Ten patients in this group were delivered in the hospital. One of these had twins.

### Treatment

As soon as possible after admission the patient with a severe toxemia of pregnancy is placed in a quiet, darkened room. If she has severe pre-eclampsia or eclampsia (which was true of all of the patients reported in this paper), a continuous spinal anesthesia is started immediately.

An initial dose of 0.5 c.c. of 1.5 per cent Metycaine solution (7.5 mg.) is then injected. The blood pressure is recorded after five minutes and again after ten minutes. After the initial recordings the blood pressure should be obtained every fifteen minutes. Subsequent injections are given at fifteen- or thirty-minute intervals. As a rule, 0.5 c.c. at fifteen-minute intervals is all that is required. We never give more than 1 c.c. unless the patient is ready for delivery. The blood pressure readings will indicate the necessity for the frequency and the amount of solution required. The smallest amount that will produce the desired effect is the proper dose to use.

A venipuncture is done and blood drawn for the following determinations: a. blood sugar, b. nonprotein nitrogen, c. uric acid, d. carbon dioxide combining power; e. total and fractional proteins, f. type, Rh and cross matching of blood. The venipuncture needle is then strapped in place.

Continuous spinal anesthesia had several advantages. After it had been started it could be continued for days, if necessary. Only small amounts of anesthetic agent (Metycaine 1.5 per cent) were needed to produce the desired effect.

Early in 1948 we decided to alter the plan of treatment of pre-eclampsia and eclampsia. Because of the excellent results obtained with continuous spinal anesthesia, the method now in use was selected. Twenty-four patients have been treated with continuous spinal anesthesia since this technique has been adopted. Twelve of these patients had severe pre-eclampsia and twelve had eclampsia with convulsions.

### Material

The Medical College of Virginia Hospitals serve a large rural area and it is natural to expect a high percentage of abnormal cases. Prior to admission to the hospital most of these patients had either no prenatal care or inadequate care. All of the patients were admitted to the ward service.

The use of continuous spinal anesthesia was withheld only when there was a definite contraindication to its use.

Table I shows the racial incidence. This corresponds with the racial distribution in ward admissions.

TABLE I. INCIDENCE IN REFERENCE TO RACE

RACE	NO. OF CASES	PERCENTAGE
White	4	16.67
Negro	20	83.33
Total	24	100.00

Table II shows the age incidence. As expected, a large percentage of the patients were less than 20 years of age. Only one patient was over 30 years.

TABLE II. INCIDENCE IN REFERENCE TO AGE

AGE IN YEARS	NO. OF CASES
14 to 15	5
15 to 20	9
20 to 25	7
25 to 30	2
30 to 35	1
Total	24

Table III shows the incidence in reference to prenatal care. Most of the patients had been seen by a doctor before they were admitted to the hospital, but they had not reported regularly either to their physician or to a prenatal clinic.

TABLE III. INCIDENCE IN REFERENCE TO PRENATAL CARE

CARE	NO. OF CASES	PER CENT
Inadequate	21	87.5
None	3	12.5
Total	24	100.0



report of the isolation of pleuropneumonia-like organisms from material from the uterine cavity. Methods used for the isolation and identification of these organisms will be reported elsewhere.<sup>9</sup> Their significance in the postpartum uterus is not definitely known, but the clinical course of the patients from whom they were isolated suggests that, at least in these cases, they were nonpathogenic. The role of pleuropneumonia-like organisms in genitourinary diseases has recently been reviewed by Dienes and associates.<sup>10</sup> They report their occurrence in 26 per cent of cervical and vaginal cultures, and conclude "the relatively high incidence of this organism in the female genital tract suggests that it is part of the normal bacterial flora in this location." Similar findings have been reported by other investigators.<sup>11, 12, 13</sup> In view of the frequent occurrence of pleuropneumonia-like organisms in the normal vagina and cervix, the isolation of these organisms from the postpartum uterus is not surprising.

Presentation of Material

As a control series, cultures were obtained from 32 postpartum patients who received no antibiotic. Of these, 27 had spontaneous deliveries and 5 were delivered by low forceps and had episiotomies (Table 7). These cases were not studied consecutively, but the cultures were obtained in the same period as those in the penicillin-treated series. That is, each time a group of patients on penicillin were cultured, a control culture was taken on an untreated patient.

Patients in the control series were selected on the basis of a normal temperature up until the time the culture was taken, since we purposely limited the investigation to the study of the bacterial flora of the normal postpartum uterus and the effect of penicillin on such flora. Cultures in the control series were obtained 36 to 72 hours after delivery.

The findings in this control group are shown in Table I. With the exception of two cases in which the cultures were sterile, the remaining 30 cases showed various bacteria, predominantly anaerobic streptococci (81.3 per cent) and *Bacteroides* (50 per cent), Table III. The penicillin sensitivity of these organisms was determined and results recorded in Table II. This reveals that the predominating organisms, anaerobic streptococci and *Bacteroides*, are highly sensitive to penicillin, while the organisms occurring less commonly are either resistant or moderately sensitive.

TABLE I. BACTERIA ISOLATED FROM UTERINE CULTURES OF CONTROL SERIES OF 32 PATIENTS WHO RECEIVED NO PENICILLIN, AND REPRESENTING THE NORMAL FLORA OF THE POSTPARTUM UTERUS

BACTERIA	NO. OF CASES	NO. OF STRAINS ISOLATED
Anaerobic gamma streptococci	23	36
Anaerobic beta streptococci	7	7
Microaerophilic gamma streptococci	2	3
Microaerophilic beta streptococci	2	2
Aerobic alpha streptococci	2	2
Aerobic gamma streptococci	1	1
<i>Streptococcus fecalis</i>	1	1
<i>Staphylococcus albus</i>	2	2
<i>Gaffkyana anaerobia</i>	3	3
<i>Bacteroides</i>	16	19
<i>Escherichia coli</i>	2	2
<i>Aerobacter aerogenes</i>	1	1
Aerobic diphtheroides	1	1
Anaerobic diphtheroides	2	2
Lactobacilli	1	1
Pleuropneumonia-like organisms	1	1
Sterile	2	

Intravenous fluids are then started through the needle already in place. The following solutions are given: a. 400 c.c. of 10 per cent dextrose solution in distilled water, b. 80 c.c. of sodium lactate solution, c. 1.2 mg. of digitoxin.

The intravenous fluids are allowed to run in slowly. A similar volume of dextrose is given every four hours until the patient can take the necessary amount by mouth. If a patient has anuria or a very limited urinary output, the volume of intravenous fluids is limited to 250 c.c. of 10 per cent glucose solution every four hours. If, after the initial blood chemistry is reported, the carbon dioxide combining power is below normal, additional sodium lactate is added to the subsequent dextrose injections. The patient should receive a maintenance dose of digitoxin (0.2 mg.) daily.

As soon as the blood pressure is controlled, the perineum is prepared for examination. A pelvic examination is done to evaluate the pelvis and to ascertain the condition of the cervix. At this time a Foley catheter is put in the bladder and it is drained every hour and the urinary output is recorded.

Special attention is given to the level of the anesthesia. It is not difficult to determine the level in a conscious patient. This is accomplished by testing the area of skin anesthesia. However, in the case of an unconscious eclamptic it is often quite difficult. In these patients the excursion of the intercostal muscles is observed closely. If there is any question about the level of anesthesia being too high further injections of Metycaine are discontinued until we are certain of the existing level.

Should the situation demand, the air passages are freed of mucus and nasal oxygen administered.

As soon as the patient becomes conscious and can cooperate, she is given 200 c.c. of sweetened fruit juice or water every hour.

When the patient is ready for delivery, additional anesthesia is needed. This is obtained by placing the patient in a sitting position and by injecting 2 c.c. of Metycaine slowly. This sitting position is maintained for thirty minutes. The level of anesthesia is then checked and, as a rule, it is adequate for delivery.

### Results, Maternal

#### 1. *Mortality.*—

Twenty-four cases were managed by the treatment outlined. There were no maternal deaths in this series.

#### 2. *Control of Blood Pressure.*—

The blood pressure was immediately lowered. As was to be expected, it rose gradually toward its former level but was quickly relowered by subsequent injections of Metycaine. After several hours, larger doses of Metycaine are required to produce the desired effect. At this point, when possible, it was found to be best to discontinue injections for one hour. When the injections were resumed the desired effect was again produced. Table VIII shows the average blood pressure obtained at the time of admission and after the spinal anesthesia had been started. It also indicates the time and amount of drug required to control the cases in our series.

#### 3. *Control of Convulsive Seizures.*—

The convulsive seizures were controlled. In our series of twelve cases of eclampsia only four seizures were encountered after the treatment had been started. One of these occurred five minutes after the initial injection was given. As indicated in Table VI, the twelve patients with eclampsia had a total of one hundred and two convulsions prior to spinal therapy. Control of the convulsions was thought to be due to the lowering of the blood pressure to a near-normal level and to the removal of stimuli incident to the pains of labor.

TABLE VIII. BLOOD PRESSURE ON ADMISSION AND AVERAGE AFTER SPINAL ANESTHESIA;  
DURATION OF SPINAL ANESTHESIA AND AMOUNT OF METYCAINE REQUIRED

CASE	BLOOD PRESSURE		DURATION OF SPINAL (HOURS)			METYCAINE IN MG.
	ON AD- MISSION	AVERAGE WITH SPINAL	PRIOR TO DELIVERY	AFTER DELIVERY	TOTAL	
<i>Pre-eclampsia.</i> —						
S. P.	170/100	140/ 90	66	3	69	750
D. W.	210/140	150/100	9	6.5	15.5	525
E. H.	170/120	130/ 90	29	28	57	420
B. J.	210/110	140/ 90	55	26	81	1,200
M. G.	175/ 95	140/ 80	8.5	23	31.5	375
J. H.	160/105	150/ 90	2.25	17.75	20	450
A. M.	200/135	150/100	34	42	76	2,310
H. P.	165/130	130/ 90	24	0	24.5	210
L. R.	165/105	140/ 90	11	2.5	13.5	300
I. S.	170/110	140/ 90	8	28	36	405
J. C.	190/130	120/ 80	5	2	7	150
C. R.	190/120	160/100	124	15	139	1,470
Average	181/116	141/ 91	31.3	16.1	47.4	713
					(Total	8,565)
<i>Eclampsia.</i> —						
S. P.	190/120	140/ 90	3	9	12	255
J. W.	170/120	140/100	24.5	0	24.5	900
E. M.	135/ 80	110/ 80	28	17	45	750
D. B.*	165/120	120/ 80	0	28	28	255
M. M.	170/ 90	140/100	45	14	59	1,305
S. W.	170/120	140/ 90	15.5	30	45.5	1,695
A. C.	150/120	120/ 90	12	13	25	375
G. C.	170/120	140/ 90	60	24	84	2,250
E. J.	148/114	140/ 90	52	0	52	1,125
M. D.	250/130	150/100	62	42	104	1,465
M. R.	200/100	150/ 90	86	1.5	87.5	1,965
B. J.*	180/100	160/100	0	52	52	1,010
Average	175/106	136/ 91	32.33	19.2	51.5	1,112
					(Total	13,350)

\*Postpartum admissions.

4. *Improvement of Urinary Output.*—

The urinary output was restored to a normal level. Hingson and Edwards attribute this to the removal of sympathetic influences thereby giving a maximum of glomerulus and afferent arterioles. It required approximately twenty-four hours to restore the output to normal proportions. Frequently, the output exceeded 4,000 c.c. for twenty-four hours and in one case it exceeded 9,000 c.c. during a similar period of time.

Six of the patients had an oliguria. Five of these were restored to normal within twelve hours; the sixth was restored in twenty-four hours.

5. *Pulmonary Edema.*—

This complication did not occur. Its absence was attributed to two things. As previously stated, these patients were all digitalized at the time they received their initial intravenous fluids. We are convinced that this procedure is very important in handling this type of patient, since nearly all of these patients have some degree of heart failure. The spinal anesthesia creates a "bloodless phlebotomy." This lessens the load on a heart that is greatly overtaxed, by pooling blood in splanchnics and lower extremities.

6. *Labor and Deliveries.*—

The presence of the continuous spinal anesthesia gave us an ideal analgesia during labor. It was because of the absence of pain, usually associated with

labor, that we were able to keep these patients quiet, comfortable, and removed from stimuli which frequently initiate convulsions. The anesthesia did not seem to either retard labor in progress or prevent induction of labor when it was indicated.

The deliveries were completed under the spinal anesthesia. The comparatively weak solution used provided only a segmental anesthesia and it was necessary to obtain additional anesthesia, as described in our technique. The anesthesia was entirely satisfactory for both vaginal and abdominal deliveries.

Table IX shows the incidence of types of delivery and fetal result. There were two multiple pregnancies (twins) in our series. As two patients were post partum at the time of admission, their babies are not included in the table. The indications for cesarean section are given and incidence of stillbirths is explained.

TABLE IX. INCIDENCE OF TYPES OF DELIVERY AND FETAL RESULT

TYPE OF DELIVERY	NO. DEL.	FETAL RESULT
Spont. vaginal delivery	6	6 live births
Forceps delivery	9	9 live births
Breech extraction	2	2 stillbirths
Version and extraction	1	1 stillbirth
Cesarean section	5	5 live births
Hysterotomy	1	1 stillbirth
	24	20 live births; 4 stillbirths

## IXA. Indications for cesarean section were:

- |  |         |
|--|---------|
| a. Fibroids obstructing birth canal          | 1       |
| b. Interruption after control of the toxemia | 2       |
| c. Primary uterine inertia                   | 1       |
| d. Premature separation of placenta          | 1       |
|  | <hr/> 5 |

## IXB. Indication for hysterotomy was:

- |   |         |
|---|---------|
| a. Interruption of pregnancy of 24 weeks complicated by eclampsia | 1       |
|   | <hr/> 1 |

## IXC. Stillbirths:

- |   |         |
|---|---------|
| a. Macerated twins, weighing 7 pounds, 3 ounces and 7 pounds, 7 ounces, were delivered in the case of E. M. There were no fetal heart tones present at the time of admission                                  | 2       |
| b. In the case of M. G. the baby was alive just prior to delivery as evidenced by the presence of fetal heart tones. The baby was delivered by breech extraction and was stillborn. Weight, 7 pounds, 1 ounce | 1       |
| c. Hysterotomy was performed in the case of M. D. for the interruption of a pregnancy of 24 weeks' duration. This produced a still-born fetus weighing 610 grams  | <hr/> 1 |
|   | 4       |

## IXD. Neonatal Deaths:

- |   |         |
|---|---------|
| a. A living baby which weighed 7 pounds, 11 ounces was delivered to A. C. with low forceps. The condition of the baby at the time of delivery was thought to be only fair. After four and one-half hours the temperature rose to 105° F. All attempts to lower the temperature failed and the baby died twelve hours after delivery | 1       |
|   | <hr/> 1 |

## 7. Additional Sedation.—

Before the effect of the spinal anesthesia can be properly evaluated, the additional sedation that was used in conjunction with it must be considered. One must also consider the amount and the frequency of each drug required for additional sedation. Small doses of Nembutal were used to combat any toxic effect of the Metycaine.

Before delivery the twenty-four patients were under continuous spinal anesthesia for a total of seven hundred sixty-three hours. During that period of time the twenty-four patients received a total of thirty-three doses of Nembutal, grains  $1\frac{1}{2}$ , or an average of  $1\frac{1}{2}$  grains every 22.8 hours. In addition, the twenty-four patients received thirty-five hypodermic injections of Dilaudid, each injection  $\frac{1}{32}$  grain. Dilaudid was administered when the patient became restless. It was given on an average of once every twenty-one and one-half hours to each patient.

After delivery we do not hesitate to use Dilaudid freely if the urinary output is normal. We usually give it every four hours during the first postpartum day. During the next twenty-four hours, it is given every six hours and discontinued altogether on the third postpartum day.

#### 8. Complications.—

There were no complications incident to the use of spinal anesthesia. We think that this is particularly significant, since it will seldom be necessary to continue treatment for a longer period of time than was used in some of our cases.

One of our patients, an eclamptic, had a severe postpartum hemorrhage. The bleeding was controlled by packing the uterine cavity with gauze. She received a total of 2,000 c.c. of blood. There was no delay in obtaining whole blood as the patients were all Rh and group typed at the time of admission to the hospital.

Three patients had an elevation of temperature above normal during the puerperium. This was attributed to endometritis. All cases cleared up promptly and the patients were discharged in ten, twelve, and fourteen days, respectively.

One patient with eclampsia, upon whom a cesarean was performed, had a disruption of her operative wound. This required a prolonged hospital stay. She was discharged on her twenty-seventh hospital day.

There were two patients with postpartum eclampsia. One of these patients developed a postpartum psychosis on her sixth hospital day. She became so violent that it was necessary to commit her to an institution.

### Results, Fetal

Fetal anoxia caused by heavy sedation with opiates and barbiturates was not encountered. These drugs were used sparingly and discontinued altogether when delivery was expected within six hours.

The babies were spared the long periods of anoxia brought about by convulsive seizures of the mother. This was borne out by the relatively good condition of most of the babies at the time of delivery.

The incidence of stillbirths and neonatal deaths with the proper corrections appears in Table X. The reasons for correction have already been given in Table IX.

TABLE X. INCIDENCE OF STILLBIRTHS AND NEONATAL DEATHS

	NO.	PERCENTAGE
Stillbirths	4	16.66
Corrected	1	4.16
Neonatal death	1	4.16
Total fetal mortality	2	8.32

### Summary and Conclusions

A report of twenty-four cases of severe pre-eclampsia and eclampsia has been presented. Twelve of the patients had convulsive seizures.

1. Maternal mortality in severe pre-eclampsia and eclampsia can be lowered by the use of continuous spinal anesthesia. There were no deaths in twenty-four cases of severe toxemia reported in this paper.

2. Fetal mortality can also be lowered by this plan of treatment. The corrected fetal mortality was 8.32 per cent, and the gross fetal mortality was 16.66 per cent.

3. Convulsive seizures were adequately controlled. Only four convulsions occurred after treatment with continuous spinal anesthesia was started.

4. The patients are easier to handle because they are conscious and are able to cooperate.

5. Continuous spinal anesthesia is an aid in restoring a normal urinary output.

6. Adequate anesthesia for both vaginal and abdominal deliveries was obtained.

7. No complications incident to the use of spinal anesthesia were encountered in this series of twenty-four patients.

8. Our series of cases is still small but we think it definitely indicates that spinal anesthesia should be further investigated in the treatment of pre-eclampsia and eclampsia.

### References

1. Ware, H. H., Jr., and Noblin, F. E.: *South. M. J.* 30: 53, 1937.
2. Ware, H. H., Jr.: *Virginia M. Monthly* 66: 456, 1939.
3. Hingson, R. A., and Edwards, W. B.: *J. A. M. A.* 123: 538, 1943.

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### Discussion

DR. WM. DURWOOD SUGGS, Richmond, Va.—In so far as I am aware, this report on the treatment of severe eclampsism represents pioneer work in this field. However, as mentioned, Hingson and Edwards in 1943 utilized the same general principles and accomplished much the same results employing continuous caudal anesthesia.

Theoretically, any relatively safe procedure which will reduce and maintain blood pressure at a lowered level, diminish external stimulation, increase urinary output, and improve circulatory stability without any depressing or other untoward effect upon the fetus until it can be delivered, would be ideal. Continuous spinal anesthesia, as employed in the twenty-four cases reported, or caudal anesthesia, seems to meet these requisites to a large degree. In addition, spinal anesthesia provides a most satisfactory anesthesia for delivery without danger of anoxia to the mother or fetus, provided the blood pressure is not permitted to drop too low. I am in agreement with the authors that continuous spinal would be safer and more practical than caudal anesthesia in the hands of most of us.

Lumbar puncture per se will reduce blood pressure in 50 per cent of pre-eclamptic and eclamptic patients according to Wieloch. He found increased intraspinal pressure, which he attributed to cerebral edema, and removed 50 c.c. of fluid. This was followed by diuresis in 38 per cent of cases.

Lundy and others have demonstrated experimentally that the fall in blood pressure is due to the blocking of the sympathetic nerve supply to the vessels below the anesthesia level. This vascular relaxation undoubtedly promotes diuresis and drains blood into the visceral vessels where it remains available to the general circulation instead of being lost as in phlebotomy.

Although the excellent results from both the maternal and fetal standpoint in this series can probably be attributed to a large degree to skillful use of continuous spinal anesthesia, the conjunctive measures employed are also important. I am inclined to feel

that the volume of intravenous fluids employed (2,400 c.c.) is excessive and would restrict the intake by 50 to 60 per cent in the presence of edema. The value of rapid digitalization was suggested by Dr. M. Pierce Rucker in January, 1931, and in subsequent reports and is widely used in Richmond and elsewhere. It probably reduces the incidence of circulatory collapse and pulmonary edema and thus secondarily improves urine output.

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Vara, Paaavo: *Studies on the Elderly Primipara*, Acta obst. gynec. Scandinav., vol. 26, supplement 2, 1946.

Vara reviews the obstetrical histories of all elderly primiparas delivered at the Women's Clinic of Helsinki in the 15-year period from 1927 to 1941, inclusive. In this group he included women aged 30 or more who were delivered of progeny weighing 600 Gm. or more. In this period there was a total of 41,634 deliveries and among these were 19,216 primiparas. Primipara cases in the ages of 30 to 34 years numbered 2,592; 35 to 39 years, 778 cases; and 40 years old or more, 197 cases—or a total of 3,567 elderly primiparas as classified by age groupings only. In 1927 the elderly primiparas appeared as about ten per cent of those bearing their first children, while in 1941 the elderly primipara was found as 25 per cent of the total primipara group of that year.

The author has a wealth of valuable and detailed data in his 133-page monograph. Only that thought most pertinent to American readers can be included in abstract form. Breech presentation was found in an incidence of 3.38 per cent. Contracted pelvis, 6.42 per cent, was a similar figure to the younger group of primiparas. The operative incidence of full-term deliveries in cases with normal pelvis was 22.4 per cent (forceps 12.5 per cent; section 4.2 per cent; other methods 5.7 per cent).

The incidence of postpartum infection was no greater in the elderly primiparous group, 15.3 per cent. Primary inertia was found in 6.8 per cent and secondary inertia in 18.2 per cent, an incidence nearly double that of the younger primipara group.

Hemorrhages were no more frequent in the older cases although soft-part ruptures were increased, first degree, 43.4 per cent; second degree, 14.2 per cent; and third degree tears, 0.7 per cent.

Maternal mortality was 0.12 per cent in spontaneous delivery group; 4.1 per cent in the operative group. The latter group showed 4.9 per cent after section and 0.7 per cent after forceps delivery. These figures were "probably" higher than in younger group.

The average weight of the babies was 3,561 Gm. The sex ratio of boys to girls in all the group of elderly primiparas was 107.05 to 100 while in women with first babies after 40 years of age the sex ratio of boys to girls was 136.6 to 100. Asphyxia was found in 7.36 per cent of deliveries. Fetal mortality was greater, 3.07 per 100. Prematurity was found in 8.52 per cent of deliveries.

The author divides his elderly primiparas into two interesting constitutional groups, (1) fully normal, and (2) presenile group. He then breaks these down into constitutional types and arrives at a new approach (probability calculus) to statistical analysis in this aspect, e.g., he found shorter and stouter women were more frequent in the operative group. This same type also had a later menarche, 15.4 years, as compared to younger primiparas.

Vara found artificial rupture of membranes done twice as frequently in the elderly group. He concludes that in addition to age factors or other complications in elderly primiparas the obstetrician must examine and manage carefully the constitutional characteristics of this group. He states the older primipara must absolutely be hospitalized. Twenty-five tables are contained in this valuable study.

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## PROLONGED LABOR\*

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*(From the Bradford Clinic)*

**P**ROLONGED labor is a progressively serious obstetrical problem fraught with maternal hardship, suffering, and potential injury. Most obstetrical texts list this entity as one of the more important predisposing causes of postpartum hemorrhage and puerperal infection, while numerous articles have been written concerning the conduct of such labor and the many factors that may contribute to a prolongation of the process of parturition. The actual delivery following a prolonged labor frequently calls for the best in obstetrical judgment and technique, both as to timing of intervention and choice of operation, for among the latter are often encountered the most formidable surgical procedures in the field of obstetrics.

This presentation constitutes an analysis and critical evaluation of eighty-five cases of prolonged labor occurring in 2,634 consecutive deliveries of white patients in a private obstetrical practice. Three and one-third per cent of these patients were in labor over thirty hours and 0.85 per cent over fifty hours.

The inability to establish with accuracy the time at which labor was initiated influences materially the reported incidence of this problem. We have attempted to eliminate in this series all cases of uterine irritability, no matter how painful, prior to the onset of regular or productive contractions and hence have established a more rigid standard of duration of labor than might be necessary. Also, a reasonably militant policy has been adopted toward the problems of both primary uterine inertia and cephalopelvic disproportion, with abdominal delivery usually being elected in such cases following trial labor of less than fifteen hours in the absence of engagement. The surgical approach to the dystocia patient earlier in labor has served to reduce the incidence of patients in labor over thirty hours in this series. The consistency of medical supervision in the hands of the authors is a contrast to larger types of clinic practice where varying attitudes toward the problem of dystocia might be adopted on different services or where even on the same service a prolonged labor problem might be handled by changing shifts of physicians.

TABLE I. AGE GROUP

Under 20 years	10	12%
20 to 29 years	44	53%
30 to 39 years	31	35%
40 years	0	

\*Read at the annual meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Va., Feb. 10 to 12, 1949.



There is no striking relationship between age and prolongation of labor in these patients. The incidence is well divided between patients in all ages of the reproductive period of life with the exception that no patient over 39 years of age was permitted to remain in labor over thirty hours.

TABLE II. METHOD OF DELIVERY

	PRIMIPARAS	MULTIPARAS	TOTAL
Spontaneous	3	5	8
Low forceps	18	7	25
Midforceps	36	4	40
Breech extraction	2	0	2
Cesarean	9	0	9
Fetal mutilation (24 weeks' gestation)	0	1	1
Total	68	17	85

There were 68 primiparas and 17 multiparas in this series. Ninety-five per cent of the primiparas eventually required an operative delivery, usually a procedure of serious difficulty, requiring evaluation and decision as to the method of greatest safety and instrumentation of the least trauma. While the history of successful vaginal delivery did not insure the physiological progress of all subsequent labors, nevertheless delivery was eventually accomplished either spontaneously or by low forceps in twelve of the seventeen multiparas.

TABLE III. MAJOR SURGICAL INTERFERENCE

	PRIMIPARAS (68)	MULTIPARAS (17)
Midforceps	56%	24%
Breech extraction	3%	0
Cesarean	13%	0
Fetal mutilation	0	6%
Total	72%	30%

The third table reveals an amazingly high incidence of major operative interference following prolongation of labor. In 72 per cent of the primiparas delivery necessitated either section, difficult midforceps or breech extraction. The one destructive operation was upon a nonviable fetus following 120 hours of labor in a multipara. It is obvious from a study of Tables II and III that the prolongation of labor, particularly in primiparas, did not solve the problem of delivery but in a high percentage of cases the passage of time presented the accoucheur with a surgical entity of major degree.

TABLE IV. CONTRIBUTING CAUSES OF PROLONGED LABOR

Cephalopelvic disproportion	40 (49%)
Occiput posterior	50 (62%)
Primary inertia	21 (26%)
Breech presentation	4 (4.7%)
Surgical induction	12 (14%)

Outstanding among the factors that might be regarded as leading to a prolongation of labor are disproportion and uterine inertia. The former was noted in nearly 50 per cent of the vertex presentations but obviously was not regarded as severe early in labor. An occiput posterior position, or transverse arrest, occurred in 50 of the 81 vertex presentations, or 62 per cent.

This emphasizes the high incidence of disturbance of normal fetal-pelvic relationship and mechanics of parturition when labor is prolonged. However, early descent of the vertex in midpelvis and the frequent use of x-rays usually gave a favorable prognosis as to ultimate delivery per vaginam. Conversely, failure of engagement usually led to recognition of more severe degrees of dis-

proportion, and section before labor became seriously prolonged. In this connection the use of x-ray pelvimetry has been of very limited value in prognosis. However, the correlation of radiologic study of the pelvis with clinical evaluation of cephalopelvic relationship, the type of labor, condition of the cervix, and other individual factors that are involved in every case of disproportion has been the usual method of obstetric deduction in this series.

Primary uterine inertia was noted in 21 cases (26 per cent). This type of desultory labor was treated by various methods including fractional Pituitrin, artificial rupture of the membranes, intravenous calcium, sedation, and general supportive measures. It is our impression that when pathological forces of this type have been in evidence for over thirty hours an establishment of frequent, regular, and productive contractions is unusual. Those patients who respond more satisfactorily to accepted methods of treatment of uterine inertia are usually delivered under thirty hours. The longer the labor the less responsive the uterus becomes to all efforts to develop the physiologic process of parturition.

The incidence of breech presentation in this series is not significant. Undoubtedly the recognition of pelvic contraction, pathological cervical dilatation, or uterine inertia when associated with a breech presentation should usually lead to delivery by section before thirty hours of labor. The four cases in this group all occurred in primiparas, two being delivered by section and two by extraction.

As a contributing cause to the prolongation of labor, surgical induction has probably not been adequately considered. Twelve patients (14 per cent) had such induction by artificial rupture of membranes, eight for toxemia and four for elective reasons. While it is granted that this complication may be reduced to a minimum by clinical evaluation of the potential labor and desisting from induction in the presence of an unfavorable cervix, or oligohydramnios, or abnormalities of presentation, nevertheless, the fact that eight cases of surgical induction for pregnancy toxemia were in labor for over thirty hours (not including the latent period following rupture of membranes) should be thought provoking. The unpredictable labor that may follow surgical induction has led to a more generous employment of abdominal section, especially in fulminating pre-eclampsia that does not improve promptly under medical therapy.

TABLE V. DURATION OF LABOR AND MORBIDITY

HOURS	CASES (85)	MORBID (15%)
30- 39	42	5 (12%)
40- 49	21	3 (14%)
50-120	22	5 (23%)

There were no severe cases of puerperal infection in the series although 20 patients were febrile during labor and 13, or 15 per cent, had puerperal morbidity (100.4° F. in any two twenty-four-hour periods following delivery). Prophylactic penicillin and sulfonamide were given to a portion of these patients as in recent years it has become our policy to administer these drugs to parturients with prolonged rupture of the membranes or prolongation of labor. The incidence of morbidity is somewhat increased as labor becomes more prolonged, although the relation of this observation must be correlated with the increased operative problem that also develops as seen in the next table.

TABLE VI. DURATION OF LABOR AND MAJOR OPERATIVE DELIVERY

HOURS	NO. OF CASES (85)	MIDFORCEPS OR CESAREAN (60%)
30- 39	42	20 (48%)
40- 49	21	11 (53%)
50-120	22	19 (85%)

The difficulties and dangers of delivery were directly proportionate to the duration of labor. Of 22 patients in labor over fifty hours, 19, or 85 per cent, had complicated and difficult operative deliveries, i.e., midforceps, destructive operation on fetus, or cesarean. Among 12 patients in labor over sixty hours (the maximum being 120 hours of labor in two instances) there were 10 exceedingly difficult operative terminations including two sections. Comparing this with an incidence of 60 per cent in the entire group of 85 patients an incidence of 48 per cent in those laboring between thirty and thirty-nine hours, the striking increase of major operative surgery for eventual delivery as labor becomes more and more prolonged is apparent.

TABLE VII. DURATION OF LABOR AND INCOMPLETE CERVICAL DILATATION

HOURS	NO. OF CASES	INCOMPLETE DILATATION OF CERVIX
30- 49	63	9 (14%)
50-60	10	4 (40%)
60-120	12	9 (75%)
Total	85	22 (26%)

The cervix failed to dilate completely in 22 patients, over one-fourth of the total number. Eight of these were eventually delivered by cesarean section and fourteen per vaginam. It is a significant fact that the incidence of failure to dilate increases directly with the duration of labor. After fifty hours 60 per cent failed ever to accomplish cervical dilatation and of those in labor over sixty hours 75 per cent were eventually delivered undilated. In such cases "more labor" will seldom accomplish dilatation. In this series of cases the problems of delivery were very rarely solved or made simpler by permitting labor to continue over fifty hours.

TABLE VIII. INFANT MORTALITY

Term deliveries	79	
Prematures	6	
Sets of twins	3	
Total infants		88
Stillbirths		2
Neonatal deaths		2
Corrected infant mortality		1 (1.1%)

One stillbirth occurred in the course of a destructive operation on a six months' fetus following 120 hours of labor. The second was a full-term child, lost during a difficult forceps extraction. This case was regarded as an error in judgment in failing to section late in labor. One neonatal death occurred from prematurity at 6 months and the second was a hydrocephalic that survived several hours following craniotomy.

There were 84 infants discharged from the hospital living and apparently well. The corrected infant mortality of only one in 85 cases of prolonged labor (1.19 per cent), in spite of the attendant complications of delivery as previously tabulated, was most surprising. Secondary to unusually good fortune numerous factors have contributed to this result including prenatal care, support during labor, selective analgesia and anesthesia, choice of operative delivery, and constant obstetrical supervision by the attending physician.

TABLE IX. MATERNAL COMPLICATIONS

Maternal deaths	0
Postpartum hemorrhage	0
Morbidity	13 (15%)

The incidence of postpartum hemorrhage and puerperal infection has generally been accepted as high following prolongation of labor. Such was not our

TABLE II. PENICILLIN SENSITIVITY\* OF BACTERIA ISOLATED FROM UTERINE CULTURES

HIGHLY SENSITIVE TO PENICILLIN†	MODERATELY SENSITIVE TO PENICILLIN‡	RESISTANT TO PENICILLIN§
Anaerobic gamma streptococci	<i>Staphylococcus albus</i>	<i>Streptococcus fecalis</i>
Anaerobic beta streptococci	Aerobic diphtheroides	<i>Escherichia coli</i>
Microaerophilic gamma streptococci	Anaerobic diphtheroides	<i>Aerobacter aerogenes</i>
Microaerophilic beta streptococci		Pleuropneumonia-like organisms
Aerobic alpha streptococci		
Aerobic gamma streptococci		
<i>Gaffkya anaerobia</i>		
<i>Bacteroides</i>		

\*Determined by the paper disc method of Bondi, A., Spaulding, E. H., Smith, D. E., and Dietz, C. D., Am. J. M. Sc. 213: 221-225, 1947.

†20 to 40 mm. zone of penicillin inhibition; sensitive to less than 0.1 unit per ml.

‡10 to 20 mm. zone of penicillin inhibition; sensitive to 0.1 to 0.4 units per ml.

§No zone of inhibition around penicillin disc.

TABLE III. SUMMARY OF THE INCIDENCE OF PREDOMINATING ORGANISMS IN THE POSTPARTUM UTERUS ON PATIENTS WITH AND WITHOUT PENICILLIN

	UNTREATED PATIENTS IN CONTROL SERIES		PENICILLIN- TREATED SERIES	
	CASES	PER CENT	CASES	PER CENT
Total cases	32	100.0	54	100.0
Sterile cultures aerobically and anaerobically (absolutely*)	2	6.2	32	59.4
Anaerobic streptococci of some type found	26	81.3	8	14.8
<i>Bacteroides</i> (anaerobic gram-negative bacilli)	16	50.0	2	3.7

\*If cultures showing pleuropneumonia-like organisms are considered as equivalent to being sterile, the percentage of sterile cultures in the control series remains 6.2 per cent, while the percentage of sterile cultures in the penicillin series becomes 74.1 per cent.

Uterine cultures were obtained from 54 patients who received penicillin therapy. The patients in this series were selected by chance, since the patients were placed on penicillin as soon as they reached the delivery floor. One-half of the series consisted of Negro women, the other of white women. Of the 54 cases, 34 delivered spontaneously (Table VII). There were thirteen patients who were delivered by elective low forceps and five by indicated low forceps, for such reasons as prolonged second stage, breech deliveries, toxemia, twins, and contracted outlets. Two patients were delivered by low cervical cesarean section. Eighteen episiotomies were performed in all. In this series, there were two cases of prolonged ruptured membranes over 24 hours, two of prolonged second stage, five cases of second degree tear, one of third degree tear, one operative induction of labor, one postpartum Pomeroy tubal ligation and one case of uterine inertia.

The amount of penicillin given the patients in this series was intentionally varied, in order to determine the smallest dosage effective in sterilizing the uterine cavity. As shown in Table IV, the largest amount was 400,000 units daily of aqueous penicillin given intramuscularly in divided doses of 50,000 units every three hours until the time the culture was taken. The smallest amount was a single intramuscular injection of 200,000 units of penicillin which the patient received on being admitted to the delivery floor. There were six miscellaneous cases which received varying dosages which did not fit into the regular groups, as shown in Table IV.

The period elapsing between the time of delivery and the time the cultures were taken was also deliberately varied, in order to determine how long the uterine cavity would remain sterile. The majority of cultures were taken between 36 and 72 hours after delivery, as shown in Table V.

occasionally under nitrous-oxide-ether anesthesia. Neither caudal nor spinal anesthesia was administered to any patients following prolongation of labor.

By far the most common surgical problem encountered was that of transverse arrest of the occiput. The Barton forceps has proved to be a most acceptable instrument for delivery in this condition. Usually a biparietal application can be obtained by which further descent and rotation may be accomplished without dangerous trauma. This forceps is frequently removed following rotation and Piper axis traction forceps applied with which heavier traction can be exerted.

In the more severe disproportion problems with much moulding and possible impaction of the vertex in the transverse position delivery may be accomplished more readily with the Kielland forceps. No cases of failed forceps occurred in this series of 85 deliveries, but there were a number of cases of error in judgment that might better have been subjected to extraperitoneal section, without persistent although usually successful efforts to accomplish delivery per vaginam.

### Summary

1. In an analysis of 2,634 consecutive deliveries of white patients from a private obstetrical practice it was found that labor was unduly prolonged in 85 cases, persisting longer, than thirty hours in 3.3 per cent and more than fifty hours in 0.84 per cent of the patients.

2. Midforceps, breech extraction, or cesarean section was necessary for delivery in 72 per cent of primiparas and 30 per cent of multiparas following such prolongation of labor.

3. After fifty hours of labor progress occurred with diminishing frequency, midforceps, destructive operation, or section being necessary in 85 per cent, and undilated cervixes persisting in 60 per cent of such cases.

4. No case of postpartum hemorrhage or serious puerperal infection occurred.

5. In this series of 85 cases of prolonged labor only one viable, normal baby was lost (1.1 per cent), and there was no maternal mortality.

6. The low incidence of postpartum complications and the satisfactory infant and maternal results herein presented indicate that prolonged labor can usually be managed successfully. However, after fifty hours of labor interference should seldom be further delayed and extraperitoneal cesarean section should be more liberally employed.

experience. There were no cases of postpartum hemorrhage. One patient with a twin pregnancy had a delayed hemorrhage at home two weeks following delivery and one patient had moderately severe bleeding from soft tissue injury sustained during a difficult forceps extraction.

In this connection the prophylactic intravenous administration of ergonovine as the vertex is delivered has been most effective in reducing hemorrhage in the third stage of labor. Prompt placental separation usually follows and excellent postpartum uterine contraction without bleeding is thereby maintained. In those cases where the placenta fails to separate promptly or becomes trapped in the cervix, manual removal is immediately accomplished. In the series of 85 cases no perineal repair was commenced prior to complete delivery of the placenta and no patient required intrauterine packing post partum.

The incidence of morbidity which has previously been discussed in its relation to duration of labor and operative delivery is not strikingly high, 15 per cent. Vaginal examinations were necessary during labor in nearly two-thirds of the cases. No routine intravaginal instillations were employed.

### Cesarean Section

There were nine cesarean sections in the 85 deliveries, an incidence of 10.6 per cent. Seven were delivered by the transperitoneal route and two were extraperitoneal. All were in primiparas, two with breech presentations, and there were no serious postoperative complications in the group. One neonatal death occurred in the hydrocephalic reported, which case was referred from a near-by city following prolonged labor.

Abdominal delivery was probably not employed as liberally as might have been indicated in view of the additional safety of the extraperitoneal operation following prolongation of labor. There are several cases here reported as delivered by difficult midforceps that would have been better handled by cesarean section and would be so handled today in the light of broader experience and more familiarity with the extraperitoneal operation.

### Discussion

The conduct of pregnancy, labor, and delivery becomes of the utmost importance when the process of parturition becomes prolonged. These private patients were for the most part in excellent condition at the onset of labor, having received and cooperated with an intensive prenatal care program. In addition to physical preparation for labor, the psychic and emotional attitude was usually good, fear complexes were at a minimum and confidence in the medical attendant was usually present. The value of this status in a patient with dystocia and prolongation of labor cannot be overemphasized.

The conduct of these labors was along accepted patterns of support and prophylaxis. Fluids in abundance by mouth and vein, together with adequate intervals of rest were supplied. In this connection morphine, either alone or following small dosage of barbiturates, was administered to 61 of the 85 patients. Demerol was used in only nine of these patients. It is our impression that the short-lived action of Demerol limits its usefulness in prolonged labor and that the restlessness and general physical depression following large and repeated doses of barbiturates preclude their continued use after labor becomes prolonged. Accordingly morphine, in adequate and repeated dosage, supplemented frequently with scopolamine, has continued to be the analgesic of choice in prolonged labor. Delivery has generally been accomplished under cyclopropane but

During the first half of the cycle, while the human uterus is under the influence of estrogen alone, the uterine contractions are of low amplitude, occur at a rate of two or three per minute and are relatively hypertonic. This pattern of motility is an intrinsic biological phenomenon related to the pituitary-ovarian cycle.<sup>1, 2</sup>

*Estrogen-Progesterone Effects.*—Following bilateral oophorectomy the uterus loses its intrinsic motility and becomes passive which indicates the essential role played by the ovarian steroids in uterine muscle physiology.<sup>1</sup> The pattern of uterine motility can be restored by the cyclic administration of estrogen and progesterone in doses simulating their endogenous production by the normal ovary (Fig. 1).

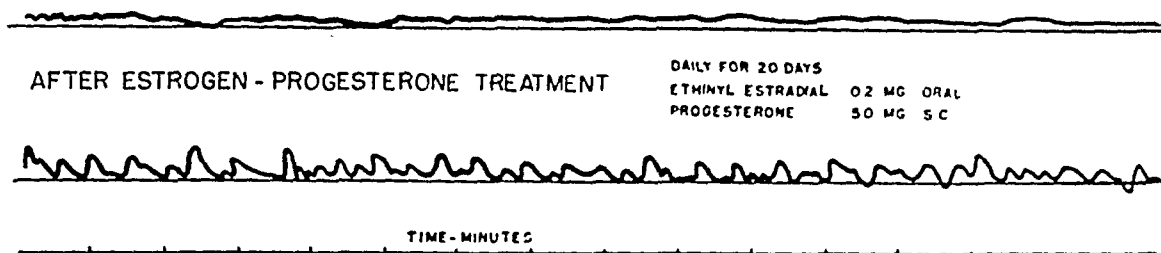


Fig. 1.—Castrate woman. Uterus is noncontractile. After estrogen-progesterone treatment the normal type of postovulatory human uterine contractions were induced.

In the patient with an intact uterus and normally functioning ovaries, the administration of estrogens does not alter the pattern of contractility during the first half of the cycle. However, if the estrogen be administered in sufficiently large doses, 5.0 mg. of stilbestrol daily throughout the cycle, ovulation will be inhibited, no corpus luteum will be formed, and the estrogen type of contractions persists. The estrogen contractions can be altered by the administration of progesterone in sufficiently large doses, 20.0 mg. daily for at least five days. It must be remembered that estrogen and progesterone are neither stimulating nor inhibitory to the myometrium in the sense that we usually construe these terms. There is a definite time interval during which the hormones must be administered (three to five days) in order to produce demonstrable effects; apparently a basic metabolic change is induced in the muscle fiber by hormone treatment.

*Pitressin and Pitocin.*<sup>2, 5, 6, 7</sup>—The nongravid human uterus reacts to the posterior pituitary principles in a very interesting and apparently paradoxical manner. During the first half of the cycle while the human uterus is under estrogen influence of the maturing follicle, the uterus is refractive to both Pitressin and Pitocin (Fig. 2). This passivity changes when the uterus comes under the influence of progesterone and estrogen (Fig. 2). During the last half of the cycle administration of Pitocin in a dose of 10 units intramuscularly occasionally induces a minimal fleeting oxytocic response, but more often has no effect upon the uterus. In contrast, the administration of Pitressin in a dose of 10 units intramuscularly during the postovulatory phase of the cycle invariably induces a marked hypertonicity and increased motility of the human uterus (Fig. 2). The myometrial spasm induced by Pitressin occurs in about three minutes after intramuscular injection and persists for a period of six to seventeen minutes. During this period of myometrial spasm the patient has all the clinical symptoms of severe dysmenorrhea. Never is Pitressin oxytocic to the uterus during the preovulatory phase, but it is invariably oxytocic during the postovulatory phase (Fig. 2). These effects of Pitressin on the human non-

## UTERINE MUSCLE PHYSIOLOGY FROM LABORATORY TO BEDSIDE, A TREACHEROUS CROSSING\*

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OUR knowledge of endocrinology and indeed all human physiology rests largely upon the conclusions drawn from experimentation with the lower animals. The clinician must yet rely upon phylogenetic forms lower than man for the advancement of his diagnostic and therapeutic endeavors. The uncritical manner in which clinicians accept the conclusions of the animal laboratory implies the presence of a broad and easily traversable span between animal and human physiology. The span is at least in part a mythical structure and grave error occurs when the conclusions of laboratory experiments along with the laboratory interpretation are brought uncritically to the bedside. The hiatus is a real one and the danger of such analogies should from time to time be brought to the attention of the physiologists and clinicians.

Satisfactory methods are now available for studying human and animal uteri in situ, thus providing a means for direct comparison of endocrine effects upon the myometrium. Perhaps no sphere of human therapy is more confused than that of endocrine therapy, particularly in relation to the human uterus. Endometrial response secondary to stimulation by the ovarian steroids in mammals is relatively constant and predictable. There are some differences resulting from the wide variations which exist in the end-artery structure of various endometriums. However, when one considers the hormones and their effect upon the myometrium as measured by uterine contraction patterns, there is little or no parallel to be found among the mammalian species.

From the clinician's viewpoint this is a problem of the first magnitude. The accommodation of the uterus to pregnancy, abortion, premature labor, parturition, expulsion of placenta, puerperal hemorrhage, uterine inertia, dysmenorrhea—to call the list of clinical syndromes related to disturbances in myometrial function is to recall our ignorance of the etiology and treatment of clinical syndromes related to myometrial dysfunction. If our understanding is to advance, we must first clear the decks of confusion and unrelated knowledge. As a starting point the comparison of animal and human uterine response to certain of the endocrines is worthy of interest.

### Hormones and the Human Myometrium

The intact human uterus has an intrinsic motility which can be demonstrated. An intrauterine balloon, connected through a closed water system to a writing point, will record the uterine contractions upon a revolving kymograph.<sup>1</sup>

\*Read at the annual meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Va., Feb. 10 to 12, 1949.



orally). The uterus is exposed and covered with saline and the rabbit is placed in a warm bath. A uterine horn is connected by means of a string to the recording apparatus, thus permitting observations of longitudinal contractions of the uterus in situ. The untreated rabbit uterus has an intrinsic motility; its contractions occur at the rate of two to three per minute (Fig. 4). It must be

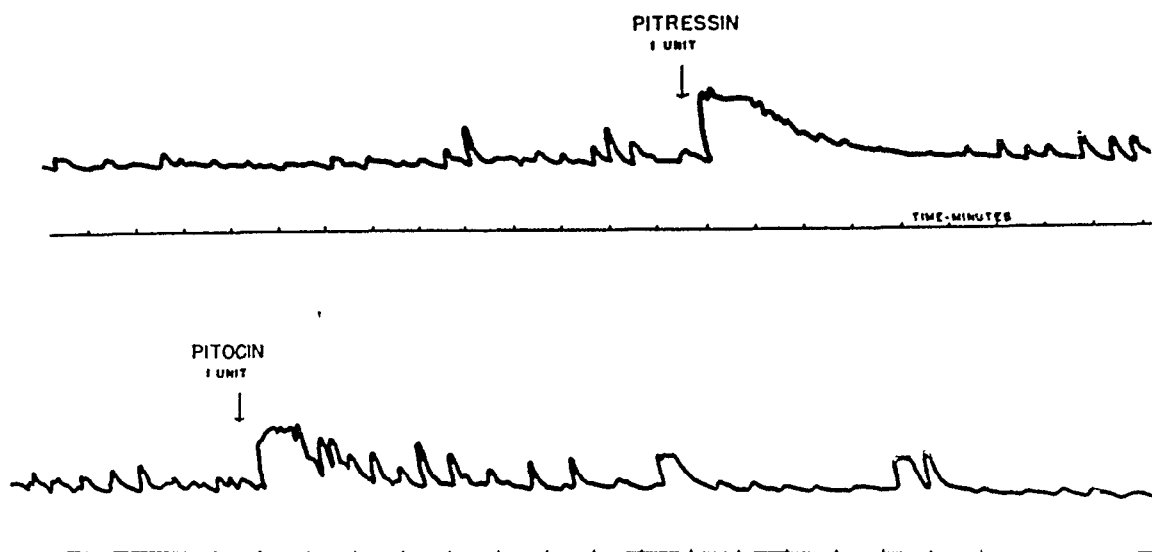


Fig. 4.—Rabbit uterus untreated. Intrinsic motility is shown. Reacts to Pitressin and Pitocin.

recalled that the rabbit, unlike the human being, is not subject to the cyclic estrogen-progesterone stimulation of the rhythmic pituitary-ovarian cycle. The rabbit ovaries are dormant and are aroused to ovulation only upon the stimulus of coitus or upon mechanical or electrical irritation. This factor places the rabbit uterus in an endocrine environment quite distinct from the human and it is not surprising that the response of the rabbit to the endocrines fails to parallel that of the human being. An estrogen (stilbestrol) was administered to rabbits in a dose of 1.0 mg. intramuscularly daily for seven days; the uterine motility was greatly augmented both in rate and in amplitude (Fig. 5). Simultaneous administration of stilbestrol (1.0 mg.) plus progesterone (5.0 mg.) daily for seven days in rabbits is followed by loss of uterine motility to the point where no contractions occur (Fig. 6). It has already been stated that the uterus of the human castrate under the influence of endogenous progesterone reacts in such a manner that the amplitude of contractions is increased while tonus and rate are reduced. Although contractions in the rabbit uterus are abolished by progesterone, the administration of this hormone to the human is followed by an increase in amplitude of the contractions and the rate is diminished. The almost unanimous acceptance of progesterone for the treatment of clinical syndromes associated with hyperirritability of the myometrium have resulted from this observation upon the rabbit uterus.<sup>4, 8</sup> There is no scientific basis for the use of progesterone in myometrial hyperirritability if it is given on the assumption that it inhibits uterine contractions, since progesterone does not reduce myometrial irritability in the human.

gravid myometrium were first observed by Woodbury<sup>2</sup> and most of his observations are here confirmed. Progesterone is apparently necessary for myometrial sensitization to the vasopressor substance.

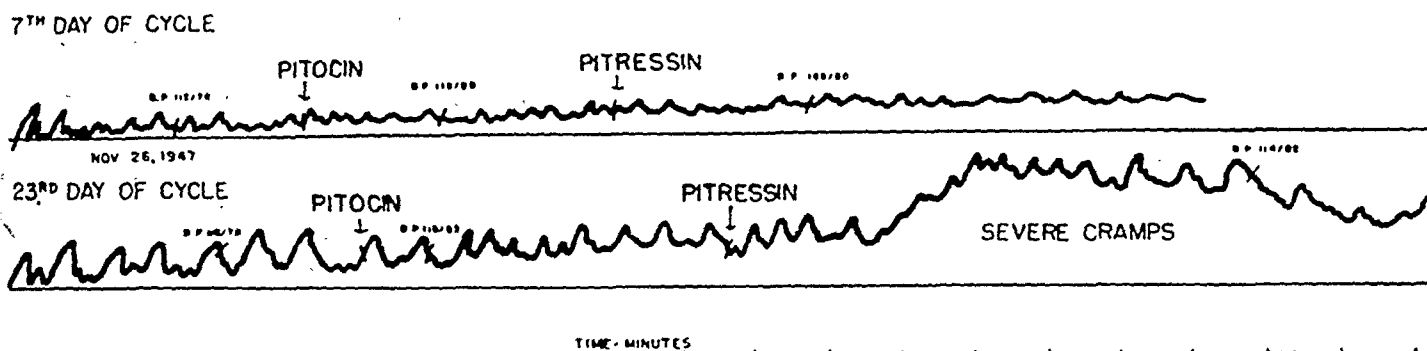


Fig. 2.—Human uterus during first half of cycle. Seventh day, normal estrogen contractions occur and uterus is refractory to Pitocin and Pitressin. During postovulatory phase of cycle, twenty-third day, contractions are normal progesterone type and uterus is relatively refractory to Pitocin, but highly sensitive to Pitressin.

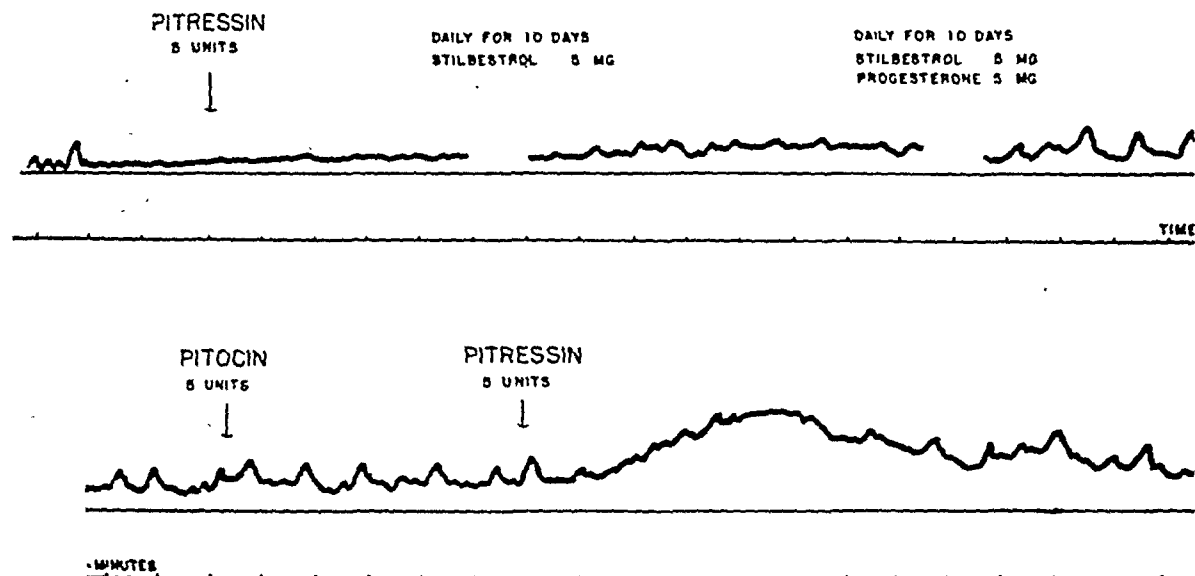


Fig. 3.—Castrate human uterus following stilbestrol-progesterone administration. Cyclic pattern of uterine contractions is induced and reaction to Pitocin and Pitressin is similar to that in the woman with intact ovaries.

The human castrate in whom all intrinsic uterine motility has been lost is refractive to stimulation either by Pitocin or by Pitressin (Fig. 3). However, if the castrate be given estrogen in the form of ethinyl-estradiol 0.2 mg. orally for twenty days and progesterone 10.0 mg. subcutaneously for ten days on the last ten days of estrogen administration, typical postovulatory type of estrogen-progesterone contractions is induced. Administration of Pitressin induces no response when given during the phase of estrogen administration alone, but it is strongly oxytocic when given during the period of estrogen-progesterone administration. This lends further evidence to the concept that progesterone is essential for the oxytocic effect of Pitressin and that it makes no difference whether the progesterone be endogenous or exogenous origin.

### Hormones and the Rabbit Myometrium

Uterine contractions of the intact uterus have been studied in the urethane-anesthetized rabbit (4 c.c. per kilogram of body weight, 25 per cent solution

### Hormones and the Guinea Pig Myometrium

The guinea pig uterus is under endocrine influences different from either the human or the rabbit. The guinea pig has regular cyclic ovulation (about eighteen days) during which time the uterus cyclically comes under the influence of estrogen. It has an intrinsic motility since it is the receptor organ for endocrine stimulation (Fig. 7).

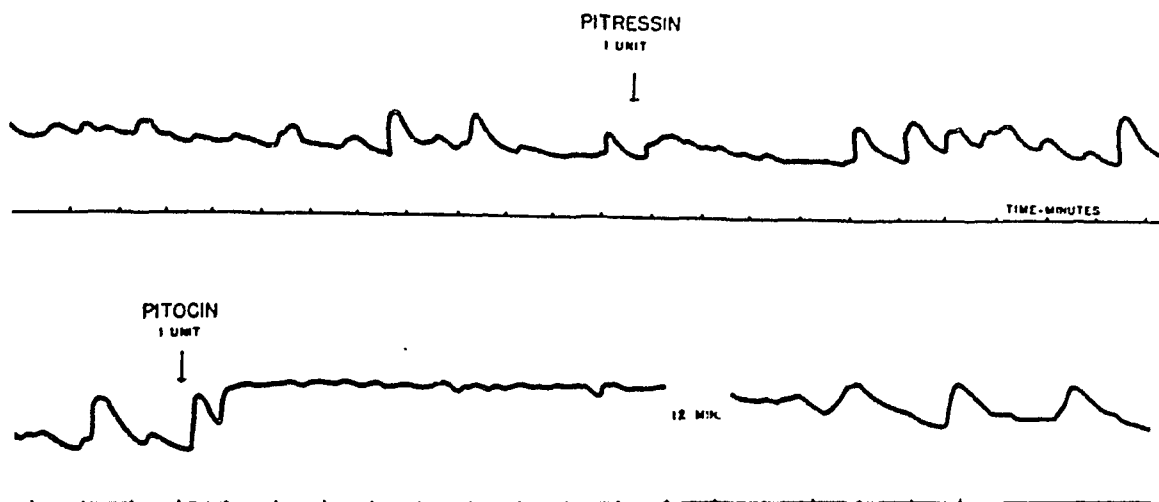


Fig. 7.—Guinea pig uterus untreated. Intrinsic motility shown. It is refractory to Pitressin and highly sensitive to Pitocin.

*Effect of Estrogen and Progesterone.*—The intact guinea pig uterus under urethane anesthesia reacts to estrogen and progesterone in a manner quite different from either the human or rabbit uterus. The untreated intact guinea pig uterus has an intrinsic motility which is more definite in pattern than that of the rabbit uterus and more closely approaches the preovulatory (estrogen) type of human myometrial contractions (Fig. 7). The contractions occur at a rate of about two per minute and have a duration of about twenty seconds which roughly parallels the human uterus, but stands in contrast to the rabbit uterus in which contractions are of very short duration, lasting barely more than ten seconds. When an estrogen (stilbestrol) is administered to the guinea pig in a dose of 0.5 mg. intramuscularly daily for seven days, all uterine motility is abolished, the uterus becomes passive, no contractions can be recorded (Fig. 8). If the guinea pig receives stilbestrol 0.5 mg. and progesterone 1.0 mg. daily for seven days, the uterus continues to remain noncontractile (Fig. 9). In its response to both estrogen and progesterone its reaction is entirely different from that of either the human being or the rabbit.

*Effect of Pitocin and Pitressin.*—The intact guinea pig uterus (urethane anesthesia 4 c.c. per kilogram of body weight, 25 per cent solution orally) is totally passive to Pitressin, but if the guinea pig be given Pitocin in a dose of 1 unit a prompt and sustained oxytocic response occurs. Commercially, Pitocin and Pitressin are checked for purity upon excised immature guinea pig uteri where Pitocin is strongly oxytocic and Pitressin is without effect. If the guinea pig now be given stilbestrol in a dose of 0.5 mg. intramuscularly daily for seven days all of its intrinsic motility is lost and it becomes refractive to both Pitocin and Pitressin. If the pig be given stilbestrol 0.5 mg. and progesterone 1.0 mg. intramuscularly daily for seven days, it is refractive to both Pitocin and Pitressin stimulation (Fig. 9).

*Effect of Pitocin and Pitressin.*—The untreated intact rabbit uterus under urethane anesthesia is highly irritable to both Pitressin and Pitocin (Fig. 4). Both Pitocin and Pitressin administered intravenously in a dose of 1 unit to the rabbit are invariably followed by a marked oxytocic response. Now if the rabbit be given stilbestrol in a dose of 1.0 mg. intramuscularly daily for seven days,

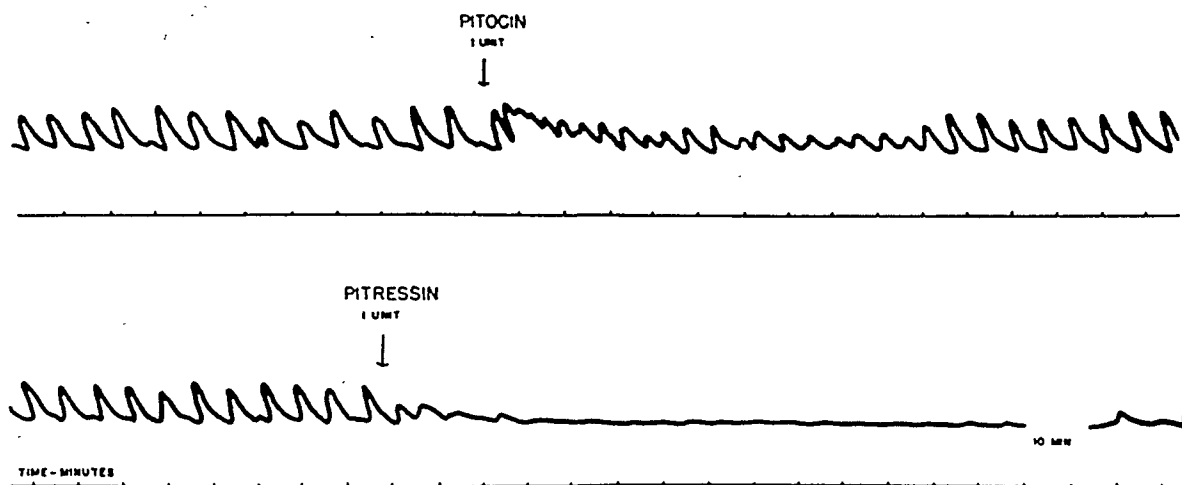


Fig. 5.—Rabbit uterus stilbestrol treated. Relatively refractory to Pitocin and completely inhibited by Pitressin.

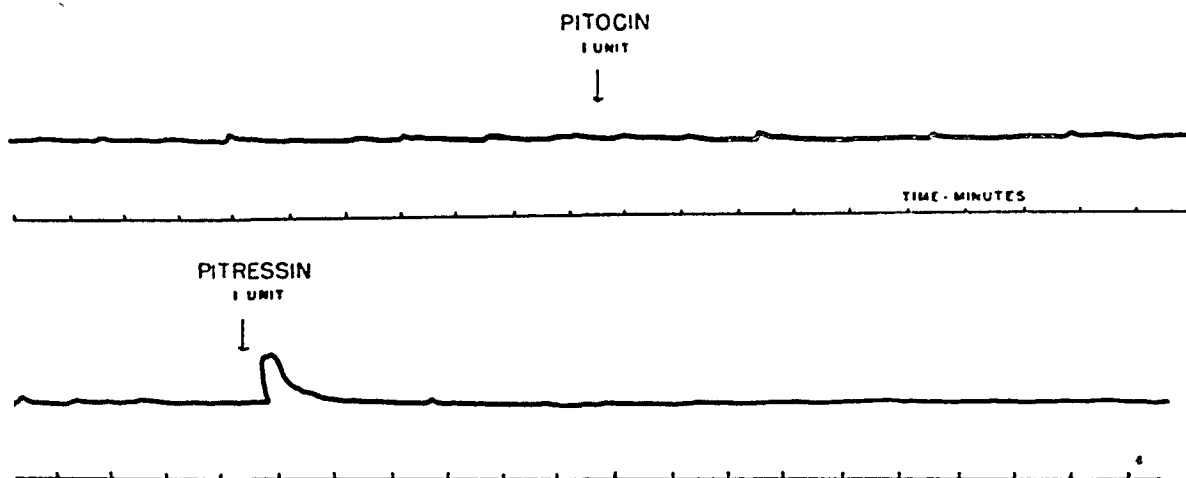


Fig. 6.—Rabbit uterus stilbestrol-progesterone treated. All uterine motility inhibited. Refractory to Pitocin and Pitressin.

there is no inhibition of uterine contraction, but its reaction to Pitocin is greatly reduced (Fig. 5). The administration of Pitressin is followed by a complete loss of motility (Fig. 5). This finding is so striking, namely, the complete obliteration of all estrogen-induced motility by Pitressin that the experiment was repeated time and again and in each experiment uterine contractions were promptly abolished only to recur after the pharmacological effect of Pitressin was expended. If the rabbit is given stilbestrol 1.0 mg. and progesterone 5.0 mg. daily for five days all the intrinsic motility of the uterus is lost; the uterus becomes totally refractive to both Pitocin and Pitressin (Fig. 6). Consider the contrast between the urethane-anesthetized rabbit and human uterus; progesterone sensitizes the human myometrium to Pitressin, while it renders the rabbit uterus insensitive to the hormone.

based on such observations, the whole fabric of hormone therapy and standardization becomes subject to some question in so far as these observations are uncritically transferred to the human being.

The human uterus has been compared pharmacologically and physiologically to that of the rabbit and guinea pig. The human uterus during the reproductive years of life is under the cyclic estrogen-progesterone cycle of the maturing follicle and the corpus luteum, the rabbit uterus is under estrogen-progesterone influence only following coitus and/or experimentally induced ovulation, the guinea pig uterus is under cyclic estrogen reaching the peak during the periods of estrus. These are important physiologic variables which probably account for, but cannot explain the species uterine reaction differences to endocrines. Rendering the rabbit and guinea pig uterus "humanlike" in its endocrine environment by cyclic administration of estrogen and estrogen-progesterone still does not bring it to a comparable physiologic state with the human uterus.

The uteri from all three species have been studied in situ; the human uterus by means of an intrauterine balloon recording the myometrial contraction and the rabbit and guinea pig under urethane anesthesia by exposure of the uterus under a saline bath. This is an essential for comparative study. Isolating uterine muscle strips from their normal vascular and nerve supply so vitiates their response as to make comparative study even more impossible. Under near physiologic conditions, the reactions of these uteri to estrogen, progesterone, Pitocin, and Pitressin have been studied and the tracings are presented. The results obtained in the three species were in such wide variance that it may be assumed to be the result of species variations in endogenously produced hormones or intrinsic differences in uterine muscle physiology patterns. An attempt was made to induce in the rabbit and guinea pig an endocrine environment comparable to that of the human by the cyclic administration of estrogen and progesterone. Although the reaction patterns to Pitocin and Pitressin were changed in the rabbit uterus toward a reaction pattern in some respects simulating that of the human being, no such shift was observed in the guinea pig.

### Conclusions

1. Patterns of uterine motility in the human menstrual cycle are well established. These are known to be related to estrogen production from the maturing follicle in the preovulatory phase of the cycle and to estrogen-progesterone from the corpus luteum in the postovulatory phase. The rabbit ovulates only upon coitus or artificial stimulation (pseudopregnancy) and has probably no intrinsic cyclic pattern of uterine motility. The guinea pig which has an estrus cycle of about eighteen days has an intrinsic cyclic pattern of motility.

2. The pattern of uterine motility in the human menstrual cycle can be reproduced in the human castrate by the cyclic administration of estrogen and progesterone, but nothing comparable to it can be induced in the rabbit or guinea pig by cyclic administration of estrogen and progesterone, at least

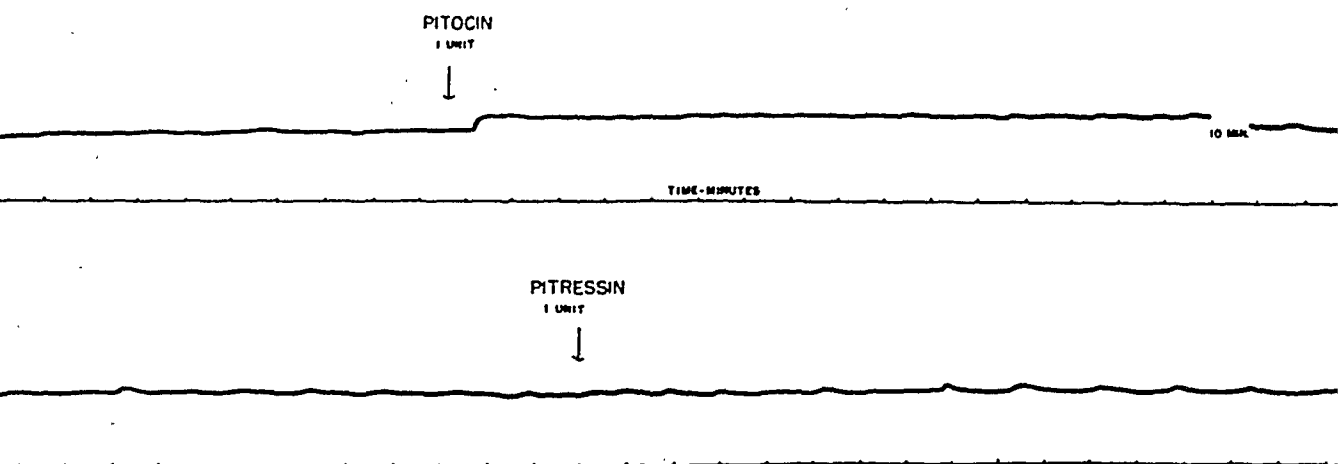


Fig. 8.—Guinea pig uterus stilbestrol treated. All motility abolished by estrogen. Refractory to Pitressin and Pitocin.

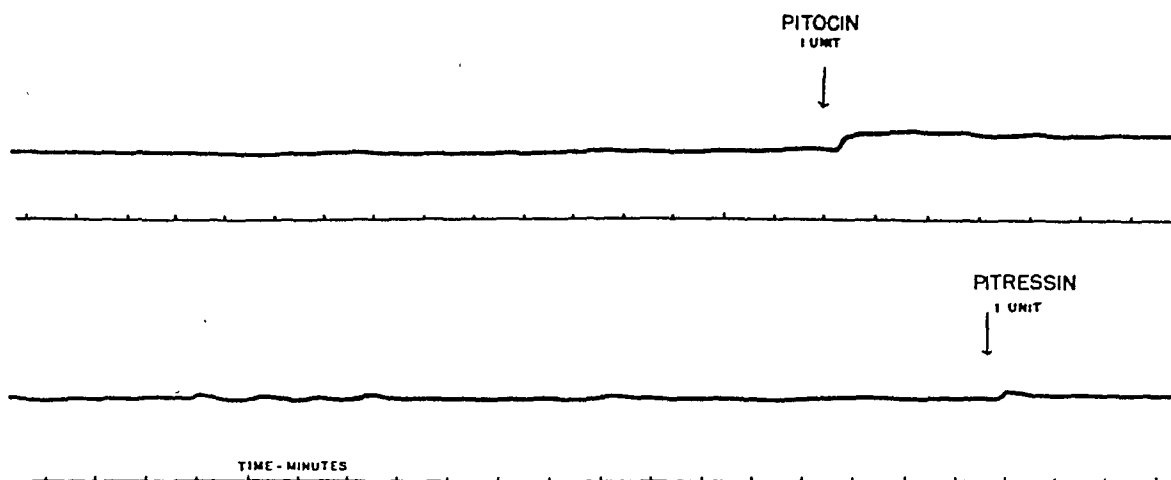


Fig. 9.—Guinea pig uterus stilbestrol-progesterone treated. All motility abolished. Slightly sensitive to Pitocin and refractory to Pitressin.

### Discussion

A review of the observations reported above reveals that the human uterus is refractive to Pitocin in all stages of the menstrual cycle, but reacts in a highly irritable fashion to Pitressin during the postovulatory phase. The intact rabbit uterus untreated reacts to both Pitressin and Pitocin whereas the administration of stilbestrol to the rabbit greatly reduces the oxytocic effect of Pitocin and makes Pitressin an inhibitor of the myometrial contractions to the point where the uterine irritability is completely lost. The administration of progesterone to the rabbit makes the uterus refractive to both Pitressin and Pitocin. The untreated guinea pig uterus is highly irritable to Pitocin, refractive to Pitressin. Stilbestrol or progesterone or both render the guinea pig insensitive to Pitressin and Pitocin.

Observations made upon the effects of estrogen and progesterone on the rabbit or guinea pig uterus cannot be duplicated by similar experiments on the human uterus. Since so much clinical therapy is based upon conclusions of the laboratory, and since indeed the standardization and dose equivalents are often

TABLE IV. BACTERIA ISOLATED FROM UTERINE CULTURES OF 54 PATIENTS RECEIVING PENICILLIN

NO. OF CASES	PENICILLIN DOSAGE (UNITS)	STERILE	PLEURO PNEUMONIA-LIKE	ANAEROBIC BETA STREP.	ANAEROBIC GAMMA STREP.	BACTEROIDES	E. COLI	AEROBACTER AEROGENES	GAFFKYA	DIPHTHEROIDES ANAEROBIC AND AEROBIC	TOTAL CASES SHOWING ALL ORGANISMS	CASES OF BACTERIA EXCLUSIVE OF PNEUMONIA-LIKE ORGANISMS
6	50,000 q. 3. h.	4	2					1			2	1
6	100,000 q. 8. h.	5		1							1	1
4	100,000 q. 12. h.	2	1				1				2	1
9	200,000 q. 24. h.	5	2				1			1	4	1
9	200,000 Stat. on Admis.	6	3	1	1				1	1	3	2
14	200,000 1 hr. PP Stat. on Admis.	6	3	3	5	2	1			1	7	7
6	Miscellaneous dosages *	4	1					1			2	1
Totals	54	32	12	5	6	2	3	2	1	3	21	14
		or	or	or	or	or	or	or	or	or	or	or
		†59.4	22.3	9.27	11.1	3.71	5.5	3.71	1.85	5.5	38.88	25.92

\*3 patients were on 50,000 units every 3 hours, stopped at delivery.

3 patients received penicillin in oil and wax, one of whom received 300,000 units every 24 hours pre-delivery only; one of whom received 300,000 units every 24 hours; one of whom received a single dose of 300,000 units on first postpartum day.

†74.07 per cent of these cases were sterile, or sterile and contained pleuropneumonia-like organisms.

TABLE V. RESULTS OF UTERINE CULTURES ON PATIENTS RECEIVING PENICILLIN CORRELATED WITH THE TIME FROM THE HOUR OF DELIVERY TO TIME THE CULTURE WAS TAKEN

HOURS FROM TIME OF DELIVERY TO TIME OF CULTURE	NUMBER OF CASES	CASES ABSOLUTELY STERILE	CASES WITH PLEURO-PNEUMONIA-LIKE ORGANISMS ONLY	CASES SHOWING OTHER ORGANISMS
0 to 24 hours	1	1	—	—
24 to 36 hours	4	3	—	1
36 to 48 hours	17	13	3	Diphtheroids only 1
48 to 72 hours	23	11	4	Anaerobic Beta Strep. Light growth after 48 hours 8
72 hrs. or more	9	4	1	4
Total cases	54	32	8	14

Total cases with pathogens 14

Total cases without pathogens 40

Percentage of sterile cases with or

without pleuropneumonia-like organisms

74.07 per cent

when measured under urethane anesthesia. Estrogen increases the irritability of the rabbit but not the guinea pig uterus; indeed, the administration of estrogen to the guinea pig renders the uterus noncontractile. Progesterone abolishes all uterine motility in the rabbit uterus and the guinea pig uterus. Estrogen increases the irritability of the human and rabbit uterus and depresses the guinea pig uterus. Progesterone increases the irritability of the human uterus and abolishes irritability in the rabbit and guinea pig uterus.

3. Pitocin is practically nonoxytocic to the human nongravid uterus both in the preovulatory and the postovulatory phase. Pitressin is strongly oxytocic to the human nongravid uterus in the postovulatory phase. The untreated rabbit uterus under urethane reacts to both Pitressin and Pitocin while the guinea pig uterus under urethane is totally passive to Pitressin, but highly irritable to Pitocin.

4. Assuming the results of laboratory experiment on the animal uterus in situ to be comparable to those of the human uterus has led to great confusion in endocrine therapy and the entire field must be critically reviewed. The development of rational endocrine therapy has been greatly retarded by the uncritical acceptance of animal experimentation. Physiologist, pharmacologist, and clinician should fuse their talents in the crucible of more intimate collaboration for the benefit of all.

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MEDICAL ARTS BUILDING

### Discussion

DR. RICHARD TORPIN, Augusta, Ga.—Dr. Bickers' emphasis that grave errors can result when data from animals are carried to the bedside without critical and careful interpretation is a well-directed observation. I am glad that he also has emphasized that estrogens and progesterone modify the threshold of the myometrium to stimuli and that these drugs should not be described as stimulative or inhibitory drugs. His results on Pitressin and Pitocin are to a large extent in agreement with those observed in human beings at the University of Georgia and the University of Tennessee. Our observations, however, do differ from those of Dr. Bickers in that we have found that the uterus will respond to Pitocin and Pitressin throughout the menstrual cycle. True, the threshold is markedly elevated during the first half of the cycle and the response to any given quantity of Pitocin and Pitressin is much smaller during the first half of the cycle. Yet the forty patients whom we have studied do show an increase in uterine activity following the intravenous administration of a small amount of Pitressin even during the first half of the cycle. In searching for an explanation for this disagreement of results, it would appear worth while to raise the question as to what quantity of fluid was placed in the balloons of Dr. Bickers' patients. In our patient 0.5 to 1.5 c.c. of fluid was placed in the balloons.



I present this slide to show the importance of the amount of fluid which is placed in the balloons. In this menstruating patient who had ovulated and whose estrogen levels were within normal range, it is possible to elicit two types of activity by placing different quantities of fluid in the balloon. Here the contractions are estrogenic in type. Here upon adding additional fluid, the progesterone type of activity results. It seems reasonable to suggest that the uterus of all patients potentially can respond by producing both of these types of activity and that the threshold of these two types of activity may be different.

The observation that estrogen and progesterone have totally different effects upon the myometrium of the human being, rabbit, and guinea pig is extremely interesting and important. I wish to call attention to the pronounced differences in dosages which Dr. Bickers used, i.e., with stilbestrol, estimating the body weight of the various animals: the daily dosages per kilogram of body weight were 80 mg. for the human being, 200 mg. for rabbits, and 1,250 mg. for guinea pigs.

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**Penttinen, Kari:** On the Wassermann and Kahn Reactions During Pregnancy, *Acta obst. et gynec. Scandinav.* 27: Supplement 3, 1946.

Penttinen, of Helsinki, in this 114-page monographic supplement reviews the serological studies on pregnant patients seen at the Maternity Center of the Women's Clinic during 1935 to 1945. In this interim, 20,145 pregnant women were seen and blood specimens were taken upon 18,090 cases (89.8 per cent). During the war years, 1941 and 1942, restrictions precluded serologic studies. In 451 cases (2.49 per cent), the Wassermann or Kahn reactions diverged from negative reports and in 393 instances full data were available. Among these series, 284 cases were regarded as "certain" cases of syphilis, 17 were "uncertain," and in 92 instances the positive syphilitic reaction was considered unrelated to syphilis.

Sixty per cent of the 284 syphilitic cases were in pregnant women aged 21 to 30 years and about 50 per cent of the group were primiparas and the other half multiparas. The positive results from cord blood of children were misleading in 28 per cent of the group.

Among the 92 false positive reactions, 70 were considered as due to technical errors (76 per cent). Pregnancy alone influencing false positive reaction was found only in fourteen cases. In all but two of the false positive reactions the positive results during pregnancy were weak, such as Wassermann, negative; and Kahn, plus one. The incidence of seropositive syphilis before the war (1935 to 1940) was 1.6 per cent, while during the war (1941 to 1944) the figure was 2.5 per cent. Wartime conditions increased the number of false positive results to 3 to 4 times as many as found under normal conditions. Thirty-three tables are included.

CLAIR E. FOLSOME.

## SIMPLIFIED GYNECOLOGIC CARE\*

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THE preparation of the gynecologic patient for operation twenty years ago was an awe-inspiring procedure. She was starved, dehydrated, and exhausted by repeated enemas until the "returns were clear." The perineum and abdomen were shaved and washed with soap and water the afternoon before. In addition, the abdomen was swabbed with alcohol and ether and covered with a sterile towel held in place by adhesive tape. Considerable effort was expended on douching, usually with a strong, antiseptic solution, in an attempt to eliminate bacteria from the vagina and perineum.

Operating room techniques were similar to those in use today, except that now we would call the caliber and quantity of suture material excessive. A double strand of chromic No. 2 catgut was the least to be used for the abdominal fascia. I have even seen chromic No. 4 catgut used by a master surgeon of the period. When silk was used, sometimes the braided strands were sufficiently strong to land a ten-pound trout! Moreover, the first assistant often would pull so tightly and enthusiastically on the continuous fascial suture, that he tended to lift the patient off the table. Stay sutures of wire or silkworm gut were commonplace and traditional, and no one thought a wound could remain intact without them. Any one of us, operated upon during that period, can remember how painfully they cut into the skin about the tenth day.

Postoperatively, the regimen was even more elaborate. Three-inch widths of overlapping adhesive tape nearly encircled the body from symphysis to xyphoid, prevented adequate chest expansion and held in place literally yards of gauze dressing. As if this were insufficient, a scultetus bandage constricted the abdomen and limited respiratory movement. If there was associated vaginal plastic operation, and multiple procedures were fashionable, a "T" binder held quantities of dressings over the perineum.

Upon return from the operating room the patient was received into an "ether" bed precisely made with flannel blankets and warmed by hot water bottles. Although the purpose was prevention of pneumonia, in effect, profuse sweating aided and abetted dehydration begun the day before. She was placed in Fowler's position with resulting interference of venous flow at the popliteal space. Small wonder that upon regaining consciousness she believed implicitly in her complete incapacitation and did not dare to move! Who among us, operated upon during that time, had the courage to overthrow these psychology and physical restraints, and move around in bed?

\*Read at the annual meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Va., Feb. 10 to 12, 1949.

The patient received no food and little fluid the first day. Sometimes crushed ice by mouth was allowed if she promised not to swallow. Water to drink was sheer poison, and intravenous infusions were uncommon. Occasionally, saline was administered by hypodermoclysis under the breasts, or in the thighs. Some clinics utilized the retention enema and gave a liter of water by rectum before the patient regained consciousness. Liquid diet might be permitted after the first twenty-four hours, but the laparotomized patient did not enjoy the privilege of a decent meal for days to come. Transfusion was invoked only upon dire necessity.

The abdominal wound was inspected frequently, but always with elaborate antibacterial techniques, including the use of sterile gloves. After careful removal of the dressings, the wound was surrounded by sterile towels and invariably swabbed with an antiseptic, before and after each manipulation. Skin clips or sutures were seldom removed before lapse of a week and silkworm-gut retention sutures remained until the twelfth or fourteenth day. The typical "railroad track" cross scars where retention sutures cut into the skin by reason of local ischemia are, alas, only too well known.

Exercise of an excretory function necessitated removal of the "T" binder and perineal dressings. Before resealing, bichloride, or other equally potent solution was poured over the perineum to re-establish the mental equanimity of nursing and medical personnel. With voiding and defecation so complicated, is there any wonder patients tended to "hold out" as long as possible? Such elaborate rituals undoubtedly inhibited the postoperative patient and increased the necessity for enemas and catheterization.

The care of the urinary bladder was a chapter in itself. Catheterization, multiple washings, frequent instillation of antiseptic and determination of the amount of residual urine were performed in utter disregard of the fact that the bladder wall muscularis and mucosa usually remained intact throughout the course of the operation. Such meddlesome interference inevitably resulted in a number of bladder infections, and not infrequently in severe cystitis. I remember a case of hemorrhagic cystitis where the mucosa of the bladder sloughed out through the urethra and the patient succumbed as a result.

Such was the pre- and postoperative care on a typical gynecologic service of twenty years ago.

### Beginnings of Simplification

Modification of such a vigorous regimen was inevitable, and by the early 1930's a few courageous souls began to doubt the necessity of some aspects of these pre- and postoperative rituals. It was realized that gynecologic surgical attack seldom involved the intestines and that starvation was, therefore, unnecessary. Similarly, it was learned that a single enema sufficed to empty the recto-sigmoid. The realization of the necessity to maintain fluid balance, both pre- and postoperatively, was undoubtedly speeded by the piteous begging of the immediately postoperative patient for water to drink. Consequently, by the middle of the fourth decade of this century, patients were allowed to eat and drink normally up to bed time of the evening before.

Also, the care of the abdominal wound was considerably simplified. In general, the trend was toward reduction of the caliber and quantity of suture material. From a personal standpoint, the biggest single step toward simplification of wound care, and requiring great courage, was elimination of stay sutures. Once this hurdle was surmounted, and the break with tradition consummated, the rest of many simplifications followed easily. Nevertheless, many a long day passed, and numerous patients were operated upon without subsequent dehiscence before we believed in actuality the doctrines we were preaching. Sutures were removed earlier following the observation that if left too long they cut into the skin and produced stitch abscesses. Fewer dressings were placed over the abdominal wound. Above everything else we learned to avoid compression of the lower ribs with adhesive tape and thus permitted free and easy expansion of the chest. Moreover, we tended to remove bandages at an earlier period than before and ultimately to use only a few pieces of gauze over the wound.

Perineal care was greatly simplified according to the ideas laid down by Plass,<sup>1</sup> and originating in 1916 with his article, "Post-Partum Care of the Perineum." Plass was able to show that "scientific neglect" gave at least as good, and perhaps better, healing than more elaborate means. Consequently, no perineal dressings, "T" binders, or pitcher douches were ever employed on any gynecologic service of my association. Even with vaginal hysterectomy, anterior, and posterior colporrhaphy, no attempt was made to achieve or maintain perineal antisepsis. Postoperatively, the region was washed with soap and water, using a clean, but not sterile, washrag, and dried with a towel.

We began to feed patients soon after operation in the belief that early resumption of normal intestinal flow tended to prevent paralytic ileus. There was some scientific basis for this, learned during efforts to make intravenous pyelograms on rabbits. The enormous colon of these animals necessitated minimizing fecal material and gas in order to obtain satisfactory films. Cathartics, enemas, starvation, and conversely extra feeding, were employed in efforts to eliminate as much gas as possible. Of all the methods, starvation produced maximal amounts of gas, since it slowed the fecal stream and encouraged growth of putrefactive bacteria. Postoperatively, intravenous fluids came into general use and sometimes the patient was allowed to drink water by mouth.

From the standpoint of prophylaxis of venous thrombosis two positive measures, and one negative, were employed. In some instances, patients were given desiccated thyroid days before operation in an effort to speed up the metabolism and the heart rate. They were encouraged to move in bed immediately postoperatively and positive orders to insure turning from side to side every few hours were issued. It finally became evident that Fowler's position, once so popular among gynecologists, encouraged stasis of blood in the popliteal space. The position is seldom employed today.

During this period of simplification of care, there came into the hospital a thin and frail 74-year-old woman with a cystic ovarian mass at least the size of a term pregnancy. She seemed to be a most promising candidate for postoperative pneumonia, at a day and time when modern "miracle" drugs were unavailable. It was obviously desirable to at-

tempt operation because of respiratory embarrassment. The tumor was successfully removed, and, with trepidation lest the wound break wide open, we lifted the patient upright into a chair the afternoon of the day of operation. By the third or fourth day she was walking to the bathroom. If a 74-year-old woman could tolerate early rising from bed why not young women also?

We learned to avoid brachial palsies when the patient was in Trendelenburg's position by removing the shoulder brace on the side of the abducted arm. A pillow under the small of the back during deep anesthesia tended to prevent loss of the lumbar curve and low back pain. Also, backaches resulting from undue flexion of the thigh upon the trunk and of the leg upon the thigh, were avoided by raising the leg holders over and above the protests of the operative assistants wishing to view the steps of a vaginal operation.

Most of these lessons were learned the "hard way," by all surgeons of the period, and no one man was responsible for the introduction of a number of them.

### Development of Simplification

The third period in my life as a gynecologic surgeon began with assumption of the directorship of a hospital service. Policies of simplification, begun elsewhere, were continued and expanded. One of the first problems to be attacked involved the amount of preliminary vaginal preparation necessary for total abdominal hysterectomy. Obviously, the way to ascertain the minimum necessary preparation was gradually to reduce to nothing. Following a series of total hysterectomies performed without previous vaginal preparation except catheterization of the urinary bladder, we found a decided increase in postoperative morbidity. Apparently, the vagina must, at least, be cleansed. Today, therefore, it is washed in the operating room with green soap and water, and dried with a sterile sponge. The term "washing" is used advisably, since the vagina is washed and not scrubbed. The urinary bladder is emptied by catheterization.

Although every effort is made to bring the patient to the operating room with proper hemoglobin and red-blood-cell values, there is sometimes unusual blood loss during the course of operation. In consequence, many laparotomized patients were transfused during the course of operation. Ultimately, the inevitable happened and an incorrectly matched blood transfusion was given to an anesthetized patient, with resulting lower nephron nephrosis. Following this unfortunate accident, we administer no transfusions to unconscious patients, except in dire emergency, since they are unable to report the beginning symptoms of incompatibility. This can hardly be classified as a step toward simplification of care, but is included for the sake of completeness.

Gradually, we learned to achieve mental equanimity regarding maintenance of postoperative fluid balance. After administration of fluids by the intravenous route became commonplace, it was inevitable that the pendulum should swing too far, and many patients suffered from overload of the vascular bed. In this instance, the doctrine of "where a little is good, more is better" does not hold true. Today, we limit the daily intravenous administration of fluid to the postoperative patient to 2,500 c.c. of isotonic solution. On the day of operation, this amount is supplemented by transfusion of quantities of blood equivalent to that

lost. Since the adoption of this policy, there has been no case of postoperative pulmonary edema.

In line with general experience throughout the world, early ambulation proved to be the best answer to the question of prophylaxis of venous thrombosis. Postoperative patients of all types are allowed up when fully conscious. We have followed this principle for more than five years. Many patients do not understand the idea of early ambulation. It should be explained to them that it is important, as soon as possible after operation, to stand or sit erect with the feet hanging down. Moreover, they must understand that early return to the erect posture does not mean forcible and permanent ejection from bed. Most patients accept the principle of early ambulation as soon as they understand that they may spend the majority of their time in bed, arising daily, but only on occasion.

As a by-product of early ambulation, the necessity for elaborate care of the urinary bladder decreased. The inability of the gynecologic patient to void stemmed from long years of inhibitory training rather than as any result of operative attack on the bladder. Because there is little need for bedpans when patients are permitted to get up at will, there is also little need for catheterization for distress. The bladder does not become overdistended, and the amount of residual urine is relatively unimportant. Actually, there are only a few gynecologic procedures where it is necessary to maintain postoperative bladder collapse. These include the Wertheim operation, vesicovaginal fistula repair, and radium application, during the time radium remains in place. We abandoned catheterization for residual urine following anterior colporrhaphy and, in fact, all other operations except the ones mentioned above. In essence, we have virtually discarded the use of the catheter and of catheterization on the gynecologic service. I might interject that this also holds true on the obstetric branch of our service.

### Care of the Wound

The most radical departure from established custom lies in our care of abdominal wounds. *Ultimately, we learned that it was impossible to manufacture a new abdominal wall with adhesive tape and sutures.* Natural processes will heal the wound firmly and strongly, provided we approximate it anatomically and accurately without constriction and with the minimum amount of suture material. Stitches in the anterior rectus fascia and throughout the closure are tied so loosely that it is possible to insert a clamp under them. Earlier, the reduction of the quantity and the duration of maintenance of dressings were mentioned. Three years ago we realized the quantity of dressings was minimal. Moreover, they were removed several days later when the skin clips were removed. On Jan. 1, 1946, we adopted the policy of employing absolutely no dressing on any abdominal wound. There are a number of theoretical advantages to the practice. First, the wound is allowed to seal itself with fibrin within a few minutes after suture. Second, the fibrin seal is a far more effective protection against bacterial invasion than gauze. Third, the moisture otherwise accumulating underneath any dressing evaporates and does not liquefy the

fibrin seal. In practice, as soon as the wound is closed it is left strictly alone. No antiseptic of any nature is put on it either in the operating room or later during the postoperative healing course.

This treatment of wounds is not such a new departure, because the policy is employed by almost all plastic surgeons and was used in gynecology years ago by Berkeley and Bonney. In their *Textbook of Gynecologic Surgery*,<sup>2</sup> they state, on page 25, "At the Middlesex Hospital we gave up all dressings for clean wounds twenty-seven years ago. A sterile towel is placed over the wound in the theatre and maintained there until the patient has recovered consciousness."

Table I shows our experience with uncovered abdominal wounds during the past three years, as contrasted with the experience of the two previous years when wounds were dressed, albeit with a minimum of gauze. It is readily seen there is virtually no difference between the two series, so far as incidence of complications is concerned. In order to test the matter still further, 100 consecutive patients submitted to laparotomy during the latter half of 1947 were studied with half of the wound dressed and the other half uncovered. The series was equalized by alternating dressing of the upper and lower half. Table II shows the result of this study. A standard sterile dressing for one-half of the wound consisted of six gauze squares, 4 by 4 inches. Skin clips closed all wounds and no retention sutures were employed. The dressing over half the wound and the skin clips were removed on the fourth postoperative day. Bacterial cultures in tryptose broth were taken both from the open and the dressed portion of the wound. The patient's reaction to the lack of dressing was recorded on the fourth day.

TABLE I. WOUND HEALING

	TYPE OF DRESSING	
	CONVENTIONAL (JAN. 1, 1944, TO DEC. 31, 1945)	NONE (JAN. 1, 1946, TO OCT. 31, 1948)
Patients, number	203	258*
Superficial separation	4	4
Infection	8	10
Dehiscence	1	1

\*In addition, 100 patients were submitted to comparative study.

TABLE II. COMPARATIVE STUDY OF 100 WOUNDS; ONLY HALF OF WOUND DRESSED

	DRESSED PORTION	OPEN PORTION
Infection, severe	4	0
Infection, slight	7	5
Slight serosanguineous exudate	3	0
Slight wound-edge separation	8	1
Granulating at 6 weeks	5	2

In general, the number of colonies of bacteria from both the dressed and open portions were similar. However, it was noteworthy that there tended to be more pathogenic bacteria underneath the dressing than on the open portion. On the open portion the organisms were more nearly of the type commonly found on skin surfaces anywhere.

Patients' opinions on the comfort of the wound were interesting. Thirty-six patients preferred no dressing, twenty-six preferred a dressing, and thirty-eight had no preference. Of the complaints, the most common included: "the skin clips catch on the bed clothes," "afraid to look at wound," "afraid wound will fall apart." Some of the comments of the examiner made at the time the dressing was removed were as follows: Covered portion of the wound, "increased

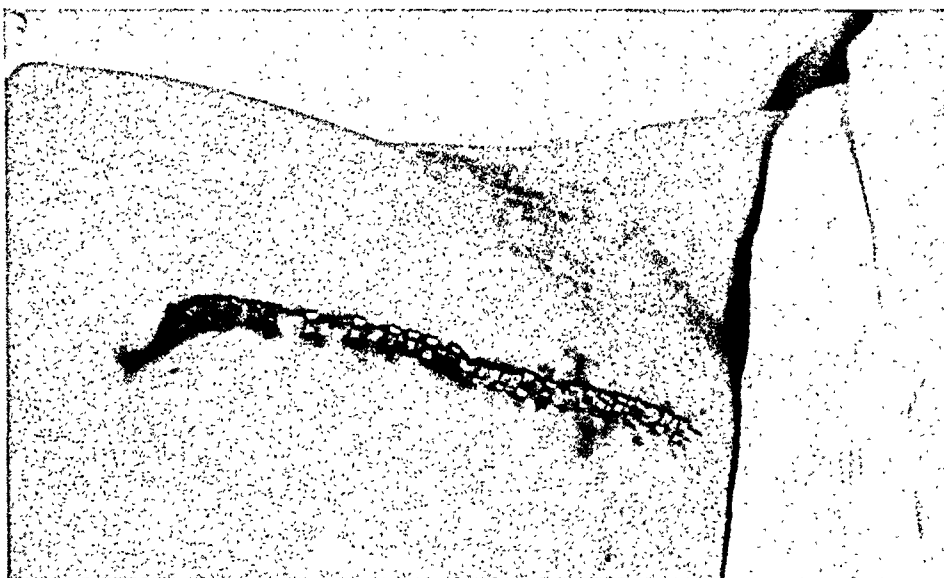


Fig. 1.—Appearance of wound twenty-four hours after operation for ruptured tubal pregnancy.



Fig. 2.—Same patient as in Fig. 1. Appearance of the wound on the third postoperative day shortly after removal of clips.

serum," "more tender," "moist, reddened, macerated, bleeds easily when dressing is removed." Open portion of the wound, "better agglutination," "stronger fibrin seal," "skin clips a little bit more difficult to remove because of the small amount of clotted blood around them." Figs. 1, 2, and 3 represent photographs made twenty-four hours after operation, on the third day, and one month later.



In essence, this story of the simplification of pre- and postoperative care parallels the period of my development as a gynecologic surgeon. As such, there is little of newness, since most of you underwent identical experiences. It was inevitable that, following the birth of modern surgery, techniques should be cumbersome and complicated, since with lack of knowledge and experience we tend to overcompensate. It is also obvious that some of our modern techniques are essential, and others persist through custom. Therefore, it is desirable to invoke a quizzical attitude, question our techniques, and constantly look for simpler methods.

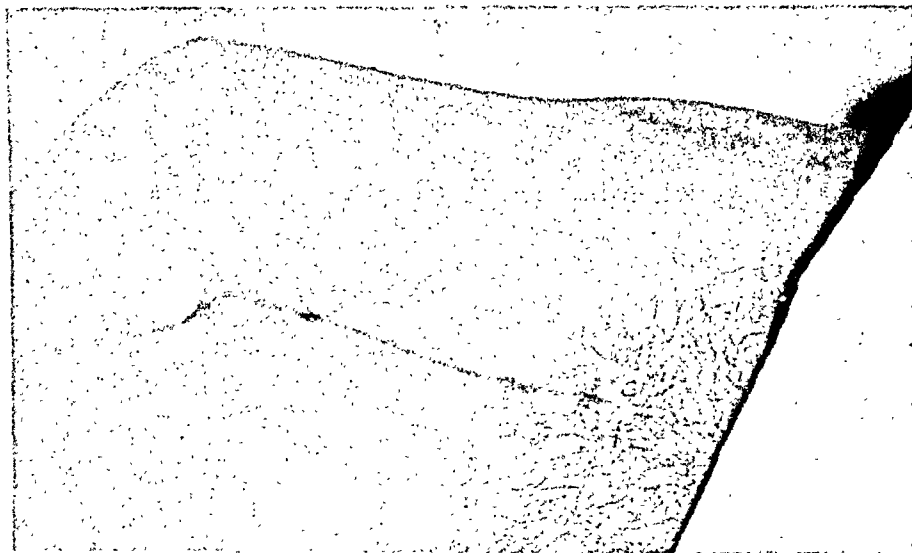


Fig. 3.—Same patient as in Fig. 1. Appearance of wound thirty days after operation.

Perhaps we have become too radical in our simplification at Parkland Hospital, especially in the care of abdominal wounds. It would be foolish to claim that leaving abdominal wounds uncovered results in greatly improved healing. Such is not the case, since the numerical differences in our two series are not sufficient to be statistically significant. On the other hand, it would seem to be permissible, from the evidence presented, to make the statement that employment of any type of antiseptic or dressing on clean, abdominal wounds is entirely unnecessary, except for the sake of adherence to time-honored custom.

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The bacteriological findings in the uterine cultures from the 54 patients receiving penicillin are shown in Table IV. Of these, 32 (59.4 per cent) were sterile aerobically and anaerobically regardless of the penicillin dosage or time of culture. In addition, 8 cases (14.8 per cent) showed only pleuropneumonia-like organisms, which are penicillin resistant and, as previously noted, probably nonpathogenic. If pleuropneumonia-like organisms be regarded as clinically insignificant, then 40 cases or 74.1 per cent of the series were free of clinically significant organisms. From a total of 22 cases various organisms were isolated, as shown in Table V, but only 14 (25.9 per cent) revealed bacteria other than those of the pleuropneumonia group. Of these, 8 cases showed anaerobic streptococci, in which anaerobic beta streptococci occurred 5 times and anaerobic gamma streptococci 6 times. As to the few other organisms isolated from patients receiving penicillin, the Gram-negative bacilli, *Escherichia coli* and *Aerobacter aerogenes*, were found to be penicillin resistant, while *Gaffkya* and the aerobic and anaerobic diphtheroids were only moderately sensitive to penicillin, and the latter are of questionable pathogenicity.

Comparison of results obtained in the two series is best demonstrated in Table III. This table shows that 6.2 per cent of the cultures in the control series were sterile, whereas 59.4 per cent of the penicillin series showed no growth aerobically or anaerobically. The predominating organisms isolated from the control cultures were anaerobic streptococci (81.3 per cent) and *Bacteroides* (50 per cent), while in the penicillin series the incidence of these organisms was 14.8 per cent and 3.7 per cent, respectively.

In Table V is presented a correlation of the cultural results and the time at which the culture was taken. Here it is shown that, as the time after delivery is lengthened, the incidence of bacterial invasion of the uterus is increased. In Table VI the 14 cases in the penicillin series which showed bacteria other than pleuropneumonia-like organisms are classified according to the amount of penicillin received and the time at which the culture was taken. This table reveals that the majority of positive cultures were obtained from those cases receiving only a single injection of 200,000 units of aqueous penicillin intramuscularly on admission to the delivery floor, and further shows that the majority of positive cultures were obtained later than 48 hours following delivery.

We believe that these 14 cases should be analyzed at this time.

In the cultures taken 24 to 36 hours after delivery, one (No. 91) contained anaerobic diphtheroids, probably nonpathogenic and only moderately sensitive to penicillin. This patient had received 200,000 units of penicillin intramuscularly, in one injection every 24 hours. She was a 15-year-old Negro girl with one living child, who delivered spontaneously, and whose only complicating factor was a first degree vaginal tear and a second degree perineal tear. In the 36 to 48 hour period, one case (No. 70) showed a late growth of anaerobic streptococci. This patient had received 100,000 units of penicillin intramuscularly every 8 hours. She was a 21-year-old Negro woman with three living children, who delivered spontaneously without unusual incident. In the 48 to 72 hour period there were 8 cases which showed organisms. Five of these received only a single injection of 200,000 units of penicillin on admission, and from all of these 5 cases anaerobic streptococci were cultured, as well as *Bacteroides* from 2 cases and diphtheroids and pleuropneumonia-like organisms from another case. All 5 of these patients delivered spontaneously without untoward incident, with the exception of one whose only complication was a second degree tear. Of the other three cases in the 48 to 72 hour group, two of these patients received 50,000 units of penicillin every 3 hours, and from these penicillin-resistant *Aerobacter aerogenes* was cultured. One of these patients was a 22-year-old Negro woman with two living children, who delivered spontaneously without untoward incident, while the other was a 34-year-old Negro woman with two living children, who delivered spontaneously after

Recently I had a check made on babies just before they were discharged, from the fourth to the seventh day. The red blood cells of 73 babies whose cords were ligated after pulsation in the umbilical arteries had ceased averaged 5,938,000 in comparison with an average of 5,657,000 of 68 babies with early ligation. The percentage of hemoglobin in the first group averaged 119.5 in comparison with 115.7 of the second group. The anesthesia of the mothers was usually vinbarbital-hyoscine and intravenous Pentothal Sodium. Since we had also changed the technique of the third stage of labor it was thought worth while to repeat our former observations.

The management of the third stage of labor is that recommended by M. E. Davis<sup>8</sup>: as soon as the anterior shoulder appears the mother is given an ampule of Ergotrate intravenously. The cord is cut between clamps as close to the vulva as convenient so as to leave as long a section of cord attached to the baby as possible. The placenta is delivered by the Brandt method as described by Andrews.<sup>9</sup> In fifty cases, selected at random, the cords were not clamped nor tied, and the placentas were delivered by Credé's method, the baby was placed in a warm bassinet and the cord was divided only after all pulsation had ceased.

It was evident that with the intravenous Ergotrate the cords ceased to pulsate sooner. In Dr. Frischkorn's and my series one cord continued to pulsate for fifty minutes and many pulsated for thirty or forty minutes. In the present series many cords had ceased pulsating before the placenta was delivered, a matter of three to four minutes. Only two continued to pulsate as long as twenty minutes, the longest interval being twenty-three minutes. As noted in the previous paper the cessation of pulsations in the umbilical vessels begins at the placenta and proceeds toward the umbilicus and when this occurs the vessels collapse. The vessels on the fetal surface of the placenta are then no longer congested.

TABLE I. RED BLOOD CELL COUNTS IN CASES OF EARLY AND LATE LIGATION OF THE UMBILICAL CORD

	EARLY LIGATION	LATE LIGATION	DIFFERENCE
No Ergotrate (333 cases)	5,198,919	(59 cases) 5,783,400	584,481
Intravenous Ergotrate, count on discharge (68 cases)	5,657,000	(73 cases) 5,938,000	281,000
Intravenous Ergotrate, count on first day (50 cases)	5,740,000	(50 cases) 5,870,000	130,000

In fifty cases in which there was early ligation of the cord the red blood cell counts of the infants varied from 4,650,000 to 6,840,000, the average being 5,740,000. The hemoglobin varied from 98 per cent to 125 per cent. The average was 113 per cent. The hemoglobin determinations were done by the micro method and 125 per cent is the highest reading on the machine. Three times the reading was reported as 125 per cent plus. Hence the average of 113 per cent is a slight understatement. In fifty cases in which the ligation of the cord was delayed until after the umbilical vessels had ceased pulsating, the red blood counts varied from 4,710,000 to 6,920,000 with an average of 5,870,000. The

## LATE LIGATION OF THE UMBILICAL CORD\*

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TEN years ago I presented to this Association the work of Dr. Frischkorn and myself<sup>1</sup> on the effect of severing the cord at varying lengths of time. We were interested in the amount of blood left in the placental vessels and the effect of this upon the red blood cell count of the infants. In 400 unselected infants delivered under Sodium Amytal, scopolamine, and ether anesthesia, the cords were clamped and cut at varying time intervals from one to fifty minutes. There was scarcely any correlation between the length of time elapsing before the cord was clamped and severed, and the infant's red blood cell count. The coefficient of correlation as figured by the Pearson formula was +0.105 and the probable error  $\pm 0.0329$ . The coefficient between the time of ligating the cord and the amount of blood left in the placental vessels was +0.2564 and the probable error  $\pm 0.0315$ . Since the coefficient is more than six times the probable error it is considered significant, although it is small. There was, as would be expected, a more significant negative correlation between the fetal red blood cell count and the amount of blood remaining in the umbilical and placental blood vessels. The coefficient of this correlation was -0.36 which is more than twelve times the probable error of  $\pm 0.0293$ . We found that whether or not the cord had ceased to pulsate was the significant factor and not the length of time that the exposed cord was allowed to pulsate. The average red blood cell count of the babies whose cords were allowed to cease pulsating before being cut was 584,481 greater than that of the babies whose cords were cut at once. We were also able to confirm the early observations of Schückling<sup>2</sup> and Haselhorst<sup>3</sup> that the baby gained approximately 100 grams in weight when the cord ceased to pulsate.

We were not impressed that the increased red blood count of one-half million made any noticeable difference to the average baby while he was in the nursery, but thought that it might make a significant difference to a premature or weak baby. We were also impressed that, in our series, the cords continued to pulsate for a longer time than in Budin's<sup>4</sup> cases, and we thought that this difference might have been due to the anesthesia that our patients received.

Since our paper was published, Windle<sup>5</sup> has noted that the infants with late ligation of the cord had 6,010,000 red blood cells and 22.1 Gm. of hemoglobin and the babies whose cords were ligated immediately, 5,450,000 and 19.5 Gm. of hemoglobin, and that this difference continued for at least the first week of life. Ballentine<sup>6</sup> has stated that the advantage of late ligation of the cord persisted until the baby left the hospital. Recently, Evans,<sup>7</sup> in discussing surgery in the newborn, stressed the advantage of this "auto transfusion" which the baby received when the ligation of the cord is delayed.

\*Read at the annual meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Va., Feb. 10 to 12, 1949.

# American Gynecological Society

Transactions of the Seventy-Second Annual Meeting,  
May 16 to 18, 1949, at Hot Springs, Virginia.

(Continued from the November issue)

## TRENDS IN THE USE OF THE CESAREAN SECTION OPERATION\*

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IN THE course of studying a series of cesarean sections performed at the Sloane Hospital during the past six years it was apparent that some interesting trends in the scope of the operation were taking place. For this reason it seemed that it might be of value to determine the nature of these trends over a longer period of time, more especially in relation to the changing attitudes toward the indications for the operation. The present survey therefore starts in 1934 and includes 1948, so that fifteen years of experience are reported.

### Gross Trend

Of interest, first, is the over-all trend for the total use of the operation. In Fig. 1, the cesarean section incidence for the larger obstetrical services in Manhattan is shown. The curve representing the total incidence of the combined services of Woman's Hospital, Sloane Hospital, New York Hospital, and Bellevue, for the years 1934 to 1948 inclusive, shows that after a fairly steady incidence just below 4 per cent up to the year 1941, there has been a definite tendency for an increased rate since that time. This combined rate has presently reached 6.2 per cent. The upward shift dates to the introduction of antibacterial therapy, which, more than any other factor, has definitely widened the scope of the operation. The inauguration of hospital blood banks came at about the same time and these, no doubt, have also played a role in this upward trend.

If the services are considered individually, the same tendency for an increasing rate since 1942 is noted in each of them but to a variable degree and from a different base. The Bellevue Service is somewhat of an exception in that the rising incidence which began there in 1944 has again returned to pre-antibiotic levels in the last two years. The New York Hospital and our own service continue to show an upward trend. At the Woman's Hospital, where the higher rate for abdominal delivery began before that of the others, a top figure was reached two years ago and their rate now seems to be leveling.

\*Presented at the Seventy-Second Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 16 to 18, 1949.

hemoglobin varied from 107 per cent to 125 per cent plus. In this series there were seven cases reported as 125 per cent plus. The average, making no allowance for the plus signs, was 116.4 per cent. The difference in the two averages of fetal red blood cells is only 130,000. This is even smaller than the difference of 280,000 which I found between early and late ligation of the cord, when the blood counts were made just before the baby left the nursery. The difference is so small as hardly to justify the more difficult technique of delivering the placenta before severing the cord.

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*(The paper, "An Evaluation of the Radical Hysterectomy in the Treatment of Carcinoma of the Cervix," by Drs. James F. Donnelly and Jesse B. Caldwell, Winston-Salem, N. C., which was also read at the Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Va., Feb. 10 to 12, 1949, will be published in the January issue.)*

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Donahue, W. L., and Fremes, I. A.: Maternal Isoimmunization Without Evidence of Clinical Erythroblastosis Fetalis in the Newborn, J. Lab. & Clin. Med. 33: 526, May, 1948.

The authors introduce their study with a discussion of the subsequent obstetrical course of women who have delivered an erythroblastotic infant and a brief review of reported cases similar to their own.

Two well-documented cases are then presented in which normal infants were delivered of isoimmunized mothers who had previously borne erythroblastotic infants. These normal infants, furthermore, possessed the proper Rh pattern for the development of this disorder in each instance. The roles of the placental barrier and Rh genetic subdivision are discussed.

S. B. GUSBERG.

Scott, J. A., and Benjamin, B.: Weight Changes in Pregnancy, The Lancet, page 550, April 10, 1948.

Monthly rates of weight gain were calculated from the records of 1,014 pregnant women on the British wartime diet supplemented by extra rations. Maximal gains occurred in the fifth (4.24 pounds) and sixth (4.70 pounds) lunar months. Thereafter, the rate gradually fell to 2.55 pounds in the last month. In this month 150 women (14.8 per cent) gained nothing. The average total weight gain was 22 pounds.

IRVING L. FRANK.

nearly all the more difficult operative deliveries will be done in this way? Is it likely that we may reach a point when vaginal procedures that require operative force will be performed only on the rarest occasions? The trend seems to be very much in that direction and unless some unforeseen factors introduce a discontinuity of the curve, we shall be practicing that kind of obstetrics within the next ten years.

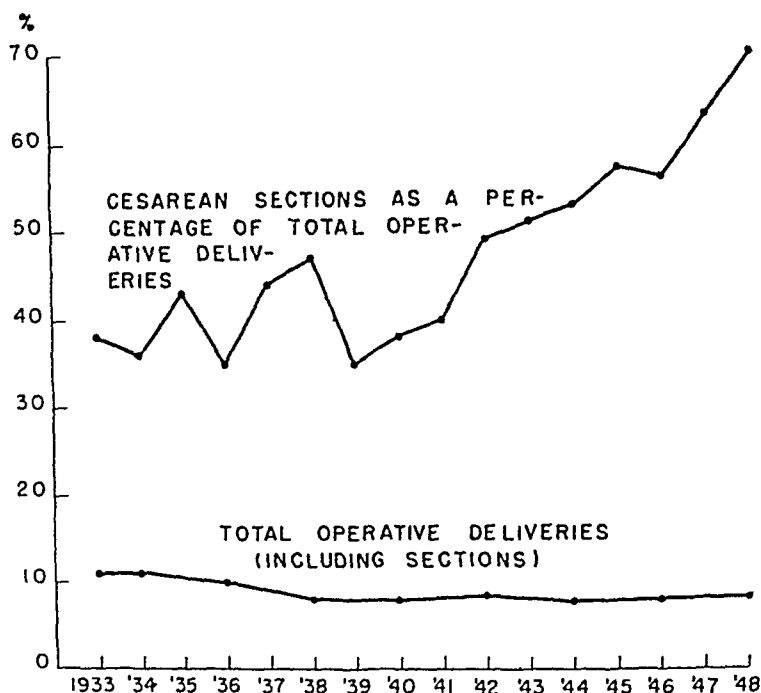


Fig. 2.

In view of these changes we should ask ourselves how they might affect the practice of obstetrics. At first thought, realizing that this eliminates much of the operative surgery of the labor room, which after all has been the stock in trade of the experienced obstetrician, it might suggest that the specialty will gradually revert to a sort of expert midwifery garnished by the cesarean operation. Let us develop this idea a little farther. The management of labor by either easy vaginal delivery on the one hand or cesarean section on the other could be achieved by adopting one of three policies. The first would aim at very broad indications for the cesarean section operation in such a manner that the operation would be done at the slightest departure from normal labor. This policy can never gain favor because there will always be an advantage in the normal delivery. The factors which make the cesarean section operation so safe today make the normal vaginal delivery even safer. Greater safety, especially to the mother, will always be inherent in the normal delivery and for that reason we will never reach a stage in the development of the specialty when the cesarean section rate may be permitted to rise with impunity. A second policy, in some ways the reverse of the first, might readily favor the operation in such obvious complications as placenta previa, but would allow long trial labors before abdominal section was done for the dystocia problems which, of course, constitute the majority of the indications. Such a policy would undoubtedly result in a desirably low section rate and, presumably, a low vaginal operative rate if desistance from vaginal operations could be practiced until a full second stage had been given. If we reach a

Assuming that a patient will return to the institution that performed the primary section, it is obvious that any broadening of the indications will result in an even greater increase in the total operations due to the repeat sections. This no doubt partially accounts for the present high rate at Woman's Hospital and will be a factor in the rates of the other hospitals during the next few years, even if there is no further change in their cesarean policies.

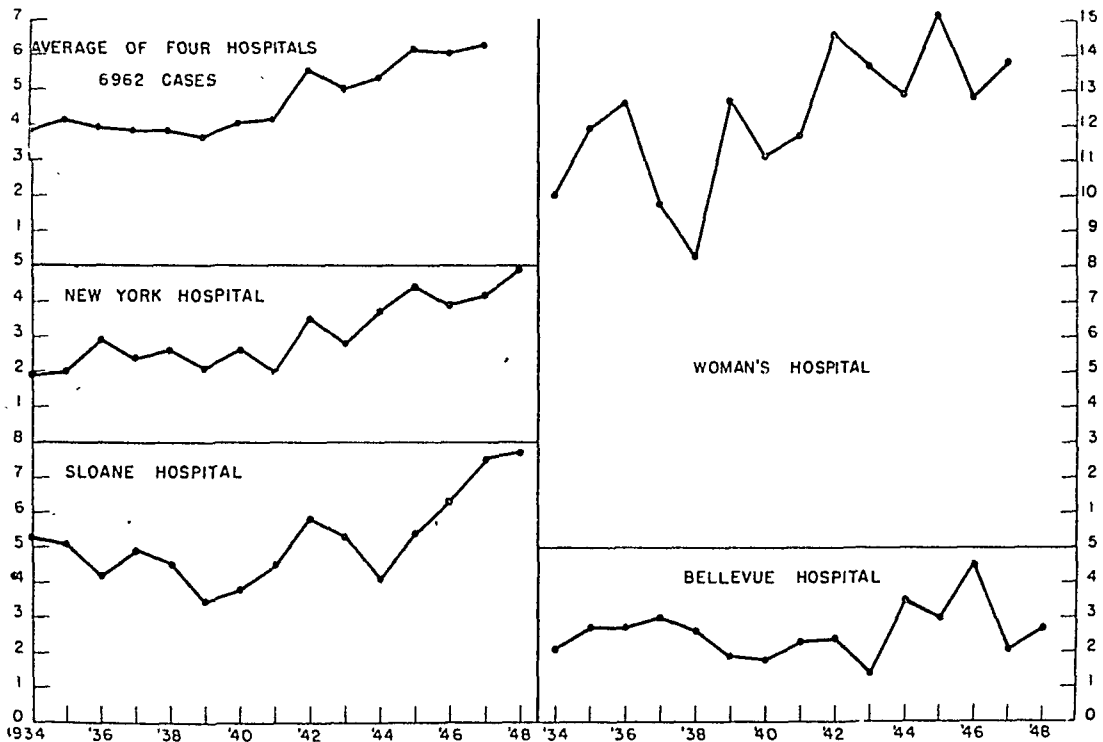


Fig. 1.

### Vaginal vs. Abdominal Operations

Another trend that deserves mention deals with the extent to which the cesarean section is replacing other vaginal operations.

In Fig. 2, operative deliveries are calculated as the total number of cesarean sections, midforceps, high forceps, breech extractions, versions—except those done for the second twin—and craniotomies. It will be noted first that there has been no increase in the total incidence of these operative deliveries. If anything, there has been a slight decrease. When the cesarean sections are calculated as a percentage of these total operative deliveries it is observed that for the past ten years there has been a slow but steady substitution of the abdominal delivery for the other obstetric operations in such a manner that, while in 1939 the cesarean sections constituted 35 per cent of the total operative deliveries, in 1948 they rose to exactly 70 per cent. Since, as already pointed out, there has been no material change in the total number of obstetric operative procedures, it follows that the cesarean section has been replacing the other operations. This substitution has been made with an extremely low maternal loss. We have performed the last 1,064 consecutive cesarean sections without a single maternal death.

It is of interest to consider for a moment the possible shape of this curve in the next ten years. If 70 per cent of the major operative deliveries are now done by the abdominal route, is it probable that at some future time



also improved. In the first half of this study there were two maternal deaths among the 138 primary sections done for cephalopelvic disproportion, and in the last half there have been no maternal deaths in the 214 sections performed for this reason.

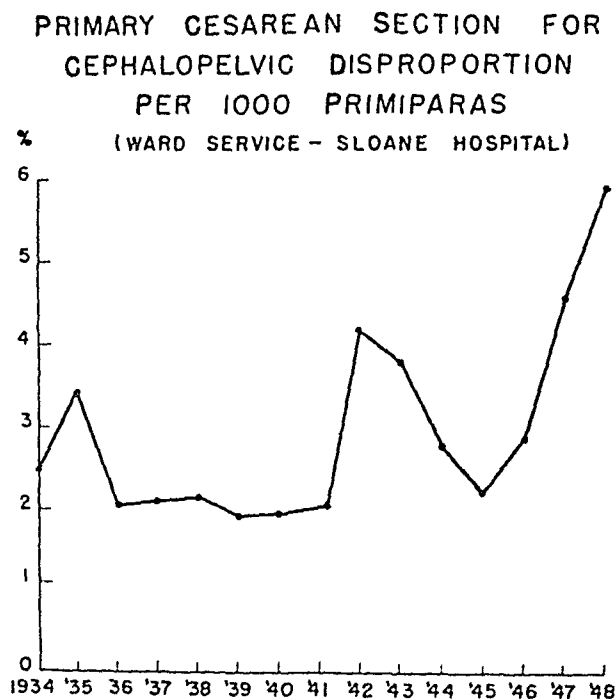


Fig. 3.

### Uterine Inertia

Frequently associated with cephalopelvic disproportion is the condition of uterine inertia. A division of these cases into three five-year periods (Table I) shows no change in the incidence of the operation with a small reduction in fetal mortality. Since it was our clinical impression that an increasing number of sections are done in this category, it is likely that the discrepancy between the figures and this impression is due to the fact that those cases of uterine inertia associated with abnormal pelvis are listed under cephalopelvic disproportion as the primary indication and therefore do not appear under this category. The two indications are not always separable.

Pituitrin infusions, which are currently employed for this condition, have not been used long enough to have had any appreciable effect on the figures, but it is likely, judging from our limited but favorable experience, that this condition, when it is not complicated by other factors, will require cesarean section less often in the future.

TABLE I. CESAREAN SECTION IN UTERINE INERTIA

	CASES	CESAREAN SECTION*	CORRECTED FETAL MORTALITY
1934-1938	292	5.1%	5.5%
1939-1943	280	6.4%	3.6%
1944-1948	224	5.3%	4.0%

\*Uterine inertia was *primary* indication.

point that permits this kind of obstetrics with safety to mother and child, we may well have the substitution of a team consisting of general practitioners and general surgeons to manage labor instead of the obstetrician. This policy may be seemingly quite practicable in view of the protection from infection afforded by the antibiotics and modern supportive therapy, and would have far-reaching effects in changing the present pattern of obstetrics as a specialty. In many quarters this policy is actually followed today but it has definite drawbacks which will keep it from gaining favor. Apart from the many prolonged and needless trial labors, it has the same deterrent argument against it that was made for the cesarean *ad lib.* policy, namely, that if these late cesarean sections can be made safe, earlier sections will be even safer to the mother and more so to the child.

A third policy, and what seems the most acceptable, would emphasize the need for better methods of prognosticating the pattern and end result of labor based on pelvic and fetal anatomical relationships and the potentialities of the contracting uterus. The obstetrician's chief interest would lie more with the problems that confront him at the beginning of labor rather than with its end. This naturally puts the emphasis more on an understanding of the physiology of labor than on obstetric surgery. With this change of viewpoint, he should develop increasingly precise tools that will enable him to determine with a high degree of accuracy the cases that will have dystocia and those that will deliver easily by their own efforts. In this way he will eliminate a great deal of vaginal obstetric surgery and still maintain a low cesarean section rate. But even before all this may be possible, the obstetrician will gradually reduce the incidence of vaginal operative deliveries by accepting a less rigid definition of cephalopelvic disproportion based on his present prognostic methods and by simply substituting the cesarean section for difficult vaginal deliveries when the occasion for such deliveries unpredictably arise.

### Disproportion

Cephalopelvic disproportion is the indication for cesarean section that is most difficult to define especially when relative degrees are considered. In order to determine the changing percentage of cases of cephalopelvic disproportion treated by cesarean section, the total number of these cases should be known—those that are sectioned, the ones that are delivered operatively per vaginam, and the group that overcome the disproportion by moulding after vigorous labor finally to deliver normally. Since this total group is not available as such from the files and for want of a more satisfactory basis of calculation, it would seem best, although not ideal, to express the changing incidence of cesarean section for disproportion as a percentage of primary sections for this indication among the total primiparas delivered. In Fig. 3 it will be noted that up to 1942 about 2 or 3 per cent of our primiparas were sectioned for disproportion. Since that time the policy in this respect has fluctuated, but within the last three years there has been a steady rise so that, in the last year, 5.8 per cent of the primiparas were so managed. Some error may be present in these figures due to the fact that the Negro group has increased from 20 per cent at the beginning of the study to 38 per cent in more recent years. While this change in the racial cross section of the cases may of itself account for part of the increase in primary sections for disproportion, it is believed that the increase is due primarily to a broadening of the policy of performing the operation in cases of relative disproportion.

Perhaps the best data to substantiate the value of such a policy is noted in the fact that cranial birth injuries, as revealed by our autopsy files, have been reduced to very nearly one per thousand births. The maternal outlook has

### Breech Presentation

As in many of the other indications for cesarean section there has been an appreciable increase in the use of the operation for breech presentation. This rise has been fairly steady through the entire fifteen years with perhaps a sharper increase since 1942. The rate for the first three years, 1934-35-36, was exactly 5 per cent, and in the last three years it has risen to 12.3 per cent, more than doubled. In evidence of the value of such a trend we note that the corrected fetal mortality rate has dropped from 7.0 per cent to 2 per cent. It is interesting to point out here one of the features associated with a rising cesarean section rate which has been in evidence through the study. It will be noted (Fig. 5) that although the incidence of cesarean section for breeches rose from 10.5 per cent in 1943-44-45, to 12.3 per cent in 1946-47-48, there was no further reduction in the corrected fetal mortality rate. This suggests that rising cesarean section rates result in diminishing returns in so far as fetal salvage is concerned. Theoretically, we can say that each indication has its top incidence figure beyond which very little is to be gained. From these figures it would seem that in our cases at least there is little to be expected by increasing the cesarean section incidence for breeches beyond ten per cent.

### CESAREAN SECTION IN BREECH PRESENTATION

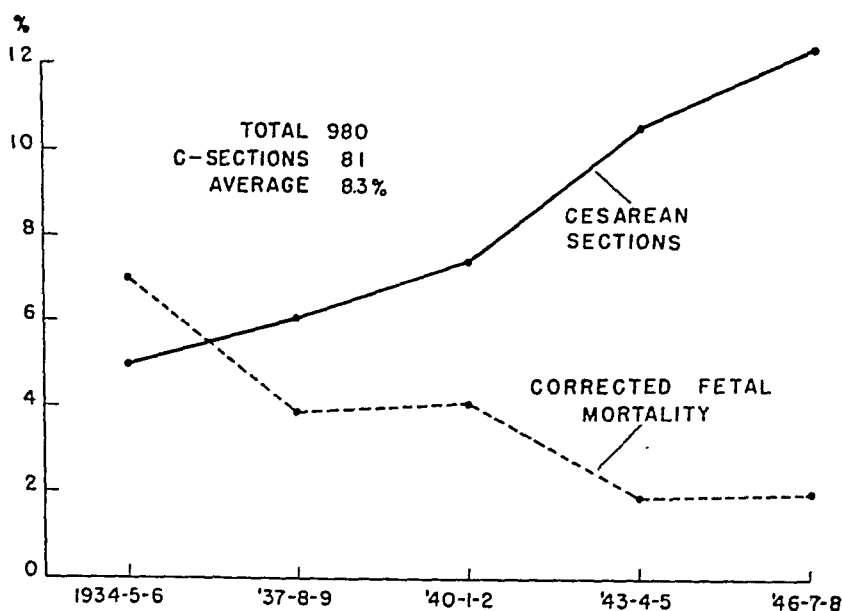


Fig. 5.

### Malpresentation

Due to the small number of cases involved, the malpresentations, which here include transverse lie, face and brow presentations, are divided into the first eight and last seven years of the study (Table II). No significant difference is noted in the rates. This may be due to the small sampling. If the last three years are considered separately the incidence of cesarean section shows an increase with a fall in the fetal mortality rate. Whether this will be substantiated in a larger series remains to be seen.

### Placenta Previa

The trend in the use of the cesarean section for the management of placenta previa indicates that this operation is being used more frequently all the time and is without any doubt the method of choice (Fig. 4). The figures indicate that it is now used in 75 per cent of the cases, where it seems to be leveling off. The one case of placenta previa out of four that is delivered vaginally is generally managed by simple measures, such as rupture of the membranes followed by spontaneous delivery. The vaginal deliveries also represent minimal degrees of the condition, with only a small amount of bleeding. Here, more than in any complication in obstetrics, we have reached the simple formula which may be expressed as: vaginal delivery without interference or cesarean section. It is not inconceivable that there will be a growing tendency to deliver all cases of placenta previa by cesarean section. One point of argument for such a policy could be based on the fetal mortality rate.

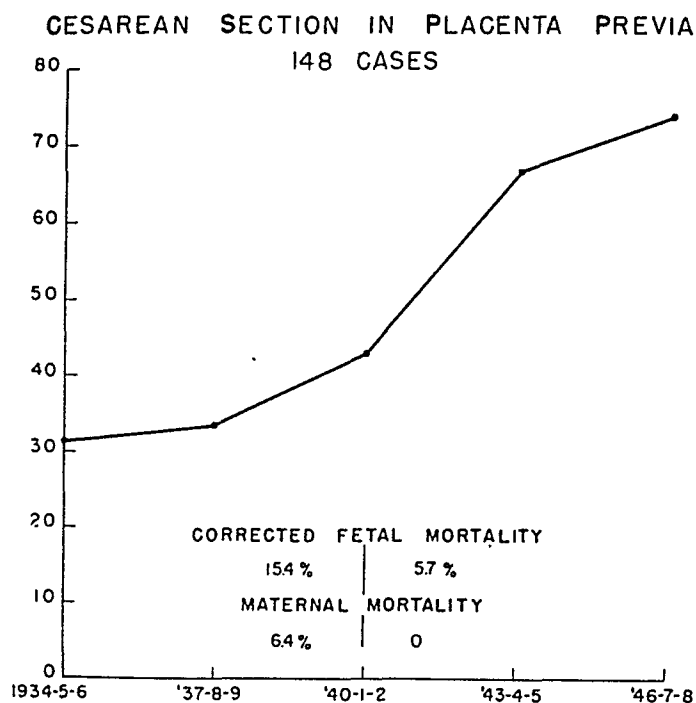


Fig. 4.

In the first half of this study this rate averaged 15.4 per cent when corrected for the congenitally malformed fetuses, antepartum intrauterine deaths, and babies that weighed less than 2,000 grams. The cesarean section incidence for this condition then averaged 30 per cent. In more recent years the fetal mortality rate corrected in the same way has dropped to 5.7 per cent. It could be argued that the fetal death rate can go still lower by treating placenta previa unequivocally by cesarean section.

Of further interest is the fact that the maternal death rate for the first half of the series was 6.4 per cent and that the six fatal cases, making up this group, were all delivered vaginally by some operative means or another. In the past nine years, following what seems to be a more conservative policy of doing either a cesarean section or uncomplicated vaginal delivery, the maternal mortality has been zero. In the past fifteen years we have not lost a single mother with placenta previa who was delivered by abdominal section.

TABLE VI. PENICILLIN SERIES: TABLE CORRELATES DOSAGE AND TIME CULTURE WAS TAKEN IN THOSE CASES SHOWING BACTERIA, EXCLUSIVE OF PLEUROPNEUMONIA-LIKE ORGANISMS

PENICILLIN DOSAGE	50,000 U. Q.3.H.	100,000 U. Q.8.H.	100,000 U. Q.12.H.	200,000 U. Q.24.H.	200,000 U. STAT. ON ADMISSION AND 200,000 U. ONE HOUR POSTPARTUM	200,000 U. STAT. ON ADMISSION
0-24 hrs.						
24-36 hrs.						
36-48 hrs.		1 Case No. 70 Light growth anaerobic beta strep.	1 Case No. 91 had diphtheroids			
48-72 hrs.	2 Cases No. 67 Aerobacter No. 44 Aerobacter	1 Case No. 73 <i>E. coli</i>	No. 27 Anaerobic gamma strep. 30 Micro. gamma strep. 97 Micro. beta strep. Anaero. gamma strep. Micro. diphtheroids Pleuron pneumonia-like 108 Anaero. gamma strep. and <i>Bacteroides</i> 107 Anaero. beta strep. <i>Bacteroides</i>	5 Cases		
72 hours		2 Cases No. 103 <i>Gaffky</i> , Anaero. diphtheroids No. 109 Anaero. gamma strep. 3 strains Anaero. beta strep. Pleuron pneumonia	No. 105 Anaero. gamma strep. Anaero. beta strep. No. 95 <i>E. coli</i>			

TABLE II. CESAREAN SECTION IN MALPRESENTATION

	CASES	PER CENT	PER CENT CORRECTED FETAL MORTALITY
1934-1941	60	25.0	10
1942-1948	72	20.8	8.3
1946-1948	22	36.4	4.5

Fibromyoma of the Uterus

Fibromyoma of the uterus in our series has been treated by cesarean section in 15.6 per cent of the cases (Table III). There has been no significant change in the trend. Three maternal deaths have occurred in this group of 576 cases. The three deaths recorded briefly occurred as follows: In 1935, laparotomy at the seventh month for acute red degeneration in a pedunculated fibroid, mistaken for a twisted ovarian cyst; death from broncho-pneumonia on the fourth day. In the same year, midforceps delivery at term followed by sepsis. In 1940, midforceps delivery; postpartum degeneration in fibroid, resulting in sepsis.

TABLE III. CESAREAN SECTION IN FIBROMYOMA

	CASES	CESAREAN SECTIONS	PER CENT
1934-1938	169	31	18.3
1939-1943	218	27	12.4
1943-1948	189	32	17.4

Prolapsed Cord

Since 1944 a new primary indication for abdominal delivery has appeared in our records (Table IV). Prior to that time the operation is not listed as a method of managing prolapse of the umbilical cord; since then eight cases are so recorded. As noted in Table IV, the corrected fetal mortality rate has been lowered from 18.9 per cent to 14.6 per cent. While this reduction in fetal mortality rate may not be proportional to the number of cesarean sections done and suggests that some of the infants delivered in this way might have been managed safely by the vaginal route, there is reason to believe that this complication will be treated by section with increasing frequency. This will be especially true when the cervix is incompletely dilated. Where minutes count this indication for abdominal section will make it mandatory that in the ideal obstetrical service the means for carrying out a rapid cesarean section be easily at hand.

The eight cases treated by cesarean section all resulted in living babies.

TABLE IV. CESAREAN SECTION FOR PROLAPSED CORD

	CASES	CESAREAN SECTIONS	CORRECTED FETAL MORTALITY
1934-1944	90	0	18.9%
1945-1948	48	8	14.6%

Cardiac Disease

Cardiac disease represents the only indication for which there is a clear-cut fall in the incidence of cesarean section (Table V). We have always been conservative in the management of these cases, but even more so in our recent experience. In the past four years we have done only one cesarean

section primarily for this condition. At one time it was felt that cesarean section, offering the possibility of sterilization, had certain advantages in selected cases but this is no longer a consideration in our present policy. Our experience confirms the fact that cardiac disease per se should never be a primary indication for the operation. We feel this way in spite of the fact that the fifteen cardiacs treated by cesarean all did well and that the three out of eight patients whose deaths occurred in the postpartum period were delivered by the vaginal route.

TABLE V. CESAREAN SECTION IN CARDIAC DISEASE

	CASES	CESAREAN SECTIONS	DEATHS FOLLOWING CESAREAN SECTION	TOTAL CARDIAC DEATHS
1934-1938	234	11	0	4
1939-1943	268	3	0	3
1944-1948	185	1	0	1

### Summary

The trend for the cesarean section operations at Sloane Hospital during the past fifteen years shows a rise in the total use of the operation which has shown no discontinuity since 1942. This agrees generally with the averaged curve presented by four of the larger obstetrical services in Manhattan, and undoubtedly represents a valid broadening of the indications for the operation consistent with the safety factors contributed by recent advances in antibacterial and antishock therapy.

The increasing trends for the operation are noted most strikingly in placenta previa, followed by cephalopelvic disproportion, and breech presentation. Uterine inertia and fibromyoma show no significant changes in their trends. Malpresentation shows a very recent upward trend. Pre-eclampsia, accidental hemorrhage, and elderly primiparity which were also studied but not detailed show very irregular and unclassifiable trends. Cardiac disease shows a definite fall in the rate of cesarean section. Finally there has been added a new indication for the operation, namely, prolapse of the umbilical cord. This condition may well show an increasing incidence in the future.

Concurrent with the increasing incidence of the operation there is a definite shift in the proportion of abdominal deliveries, when compared to the number of vaginal operations. This is even more significant because there has been no change in the total number of all operative deliveries. The implication of this trend is that obstetrics is moving away from the area of vaginal obstetric surgery toward abdominal delivery. In support of this it can be shown that under ideal conditions the abdominal delivery is not more hazardous to the mother than the difficult vaginal operations and is certainly less traumatizing. The risk to the child is decreased as well. Against this trend it may be said that it will lead to unnecessary cesarean sections that are done when a vaginal delivery could have been effected easily and safely for both mother and child. Since it is axiomatic that uncomplicated vaginal deliveries will always be safer than abdominal deliveries, these unnecessary sections done for convenience or because of ignorance cannot be justified.

## Discussion

DR. E. D. PLASS, Iowa City, Ia.—With such a reduction in the risk from abdominal delivery as has materialized during this past generation, it was inevitable that there would be some relaxation in indications for the operation. In my clinic the incidence of cesarean section has risen from 1.0 or 1.5 per cent to 4.0 per cent during the past twenty-three years, and I believe the increase has been justified and reasonable. By eliminating the physically difficult and mutilating vaginal deliveries that were so disastrous to both the mother and her child, the operation has served a specific and beneficial purpose.

On the other hand, no one has yet had the temerity to propose that all women be delivered abdominally, a tacit admission that cesarean section is more dangerous than vaginal delivery. Statistical data now available support the belief that neither the maternal nor the child mortality of abdominal delivery can be reduced to that of normal vaginal delivery. We are, then, confronted with what the economist recognizes as "the theory of diminishing returns"—there must be a point beyond which the lives and health of pregnant women and their children as a group would be prejudiced by further relaxation of the indications for cesarean section. Where this point lies would obviously provoke argument, but I am inclined, in view of our present information, to place it in the neighborhood of 5 per cent.

Another phase of the problem concerns the growing tendency to substitute abdominal delivery for induction of labor whenever an acute complication demands interruption of pregnancy, even though the latter is generally effective and certainly safer. When the complication is not likely to recur in a subsequent gestation, the use of abdominal delivery would seem rarely to be justified since it reduces the woman to what some have called an "obstetric cripple," an expression that emphasizes not only the artificial weakness of the uterine wall but also the mental state that militates against much further increase in the size of the family. Most women do not want more than two or three children, when the birth of each child demands a major abdominal operation, and many feel that one such experience is enough. The sociologic implications of families that do not provide numerical replacement of the breeding stock, the parents, are obvious.

Since many of the recognized indications for abdominal delivery are essentially fetal in nature, I must confess some curiosity about the total uncorrected child mortality in Dr. D'Esopo's series. I inherently dislike corrected statistics, and particularly in cesarean section, where the indication for the operative intervention is so often fetal. I would be inclined to view the extraction of a child with a congenital anomaly incompatible with extra-uterine existence or of a nonviable premature infant as a therapeutic failure, unless the operation were actually life-saving for the mother, and there are really few such instances.

We should then, I feel, be cautious about lending the prestige of this Society to any marked and sudden extension of the indications for cesarean section beyond the point where the operation truly serves the best interests of the two patients involved.

DR. W. C. DANFORTH, Evanston, Ill.—I wish to present some figures concerning cesarean section from our service at the Evanston Hospital. These figures are taken from a study of the last 20,000 cases which was made by my colleague, Dr. R. M. Grier. The number is actually 20,811. The great majority of these were private patients. The staff consists wholly of obstetricians who are members of the Department of Gynecology and Obstetrics of Northwestern University. I am in accord with the opinion which has come from a number of clinics in the past two or three years, that cesarean section should be used more liberally in the management of placenta previa. But there is too great a tendency in some places to broaden the indications too greatly. In a recent visit in a large city I was told by a member of the obstetrical staff of a hospital which is regarded in that city as one of the best, that the incidence of cesarean section in that institution varied from year to year from ten to twelve per cent. This seems entirely out of line and would indicate that many problems are being solved by section which might be dealt with by other obstetrical means.

In the 20,811 cases in our service there were 856 sections, or 3.26 per cent. The maternal mortality in this series of sections was 0.93 per cent.



Many physicians, chiefly those whose obstetrical experience is not extensive, seem to feel that abdominal delivery is a rather certain way of obtaining a living child. Because of the indications for which many sections are done this cannot be so. Abruptio placentae, placenta previa, and severe toxemia take an inevitable toll. The fetal mortality in the group of sections was 8.2 per cent. This may be compared with the fetal mortality after midforceps operations, for example. This was 2.2 per cent. That operative delivery was not avoided may be indicated by the incidence of outlet forceps delivery which was 50.2 per cent.

Cesarean section is an operation of tremendous importance. This fact, however, should not cause us to advocate it when sufficient indications do not exist. The mortality of section, even in well-staffed institutions, is usually somewhat greater than that of major abdominal gynecological procedures. While our mortality rate of 0.93 per cent is a satisfactory figure it still is higher than our mortality in either total abdominal or vaginal hysterectomy. In a few cases only delivery through the vagina was permitted after cesarean section. Our over-all obstetric mortality in this group, including all operative procedures, and including some deaths from disease present during pregnancy and parturition, was 0.091 per cent. While the danger of cesarean section is notably less than it was years ago, it is still an operation which carries an appreciable mortality. While I am fully appreciative of its worth, and we are all convinced that we cannot do without it, I would express a word of caution concerning a too great broadening of indications.

DR. EDWARD A. SCHUMANN, Philadelphia, Pa.—Whenever, I hear a paper like this thoughtful, philosophical presentation of Dr. D'Esopo, I am mentally torn by the chart showing the tremendous number of cesarean sections done in another clinic and I wonder if in my own clinic possibly a similar chart would reveal not quite enough sections done. As I watched Dr. D'Esopo's graphs I was impressed by the 6 per cent incidence of section for cephalopelvic disproportion. Frankly, I do not believe that cephalopelvic disproportion of appreciable degree exists in 6 per cent. I think a little teaching of the mechanism of labor to our medical students might lower this indication markedly.

I am in entire accord with what Dr. Danforth has said about cesarean section in the presence of hemorrhage. Section incidence cannot rise too high in severe placenta previa to suit my own idea.

There are two points I should like to emphasize: cesarean section in the presence of malpresentation and cesarean section in the presence of a dead baby. Dr. Plass has spoken of the therapeutic failure if a dead baby were delivered by cesarean section. That in general is quite true, but what about the neglected, impacted transverse presentation in a patient who has had attempts at delivery from below and finally arrives at the clinic a bad surgical risk? She often is also a bad obstetric risk with a dead baby, and I have yet to see the obstetrician, be he young or old, trained or untrained, who has had sufficient experience with difficult embryotomies to do them well. This is a formidable procedure at best and, after the passage of one or two hours, one may find that the patient is in serious condition from shock and blood loss and exhaustion, and embryotomy may or may not have yet been accomplished. With the enormous improvement in surgical technique through extraperitoneal section it is in our experience—and we now have some twenty-six cases to record—a perfectly safe procedure for the mother to do an extraperitoneal cesarean on a dead impacted transversely presenting baby, to extract the baby through the uterine incision by embryotomy, if you please, under the eyes without difficulty, with much less risk to the mother, and I advocate this procedure in this indication.

I fear we are a little "loose" with our cesarean sections. It is so perfectly simple to do the operation under local anesthesia two, three, or four times. I find that these patients who have been operated upon under local anesthesia do not object to repeat sections, but I do believe that we must guard against too ready a tendency to perform cesarean section in the presence of a very dubious cephalopelvic disproportion,

DR. NORMAN F. MILLER, Ann Arbor, Mich.—I would like to ask the essayist what he does with the fibromyomas for which cesarean section was indicated?

DR. GEORGE KAMPERMAN, Detroit, Mich.—Having been trained as a conservative by a conservative teacher, it has been very difficult for me to rid myself of conservatism and I must confess that I have resisted a great many of the procedures that took us away from conservatism. I have embraced some of the ideas of the newer obstetrics, but I feel resistant toward becoming too radical.

I have often seen the indications for cesarean section labeled after the performing of this operation. I would make a plea for more careful preoperative diagnosis of the indications. For instance, too often cesarean sections are performed for bleeding without a precise diagnosis of the cause of the bleeding. The fact that occasionally the roentgenologist does not properly diagnose the position of the placenta gives some obstetricians the attitude that roentgenologic examination does not mean much, and they are afraid not to operate. The same is true of cephalopelvic disproportion. A patient may have labored for a long time and disproportion comes into the mind of the obstetrician. In fact, it amounts to a fear in the minds of many men. The cesarean section is then performed just because of fear. It takes a great deal of experience to develop good judgment and fortitude so as not to be led into these radical operative methods simply because we are afraid.

DR. JOSEPH L. BAER, Chicago, Ill.—There are a few points which we carry out in our institution which I think it might be well to convey; most of you probably do the same things but lest you do not I want to emphasize them.

The cephalopelvic disproportion group is always debatable. We have an inviolable regulation in our department at Michael Reese Hospital that at the time of section the inlet must be measured while the abdomen is open and the biparietal measurement of the fetal head is taken immediately after delivery. At the regular monthly meeting of our department every cesarean section is analyzed in detail and particularly as to the indications. We emphasize the necessity for a recorded preoperative indication before a patient is subjected to cesarean section. It happens that every once in a while our cesarean section percentage goes up, and after the following monthly analysis it goes down.

I believe that cesarean section for any indication whatsoever without a vaginal examination is subject to incomplete preoperative diagnosis. We refuse to be intimidated by the anxiety that accompanies a vaginal examination preceding cesarean section. And we not only permit it; we insist upon it.

DR. NELSON B. SACKETT, New York, N. Y. (By invitation).—I would like to make one comment concerning the value of extraperitoneal cesarean section in cervical dystocia cases. I know I am on dangerous ground in using that word. In 1940 I reported the incidence of true cervical dystocia. In 8,000 confinements in Woman's Hospital in New York, I threw out seven out of eight so-called cervical dystocia cases and retained one per cent, or 80 cases of true cervical dystocia.

Along with Dr. Schumann, I would like to put in a plea for the use of extraperitoneal cesarean section in these cases. I feel that having the extraperitoneal cesarean section "up your sleeve" enables you to exercise conservatism along the line Dr. Kampermann mentioned: to have the courage to let the patient labor on a few hours longer, knowing that you can still get out of a bad situation with extraperitoneal cesarean section. My study in 1940 showed that most of these patients were safely delivered from below, usually by medium forceps and occasionally with the blades inside the cervix. In those cases where we guessed wrong, the extraperitoneal cesarean section gave excellent results for mother and baby.

DR. D'ESOPPO (Closing).—I am inclined to agree with Dr. Plass that the cesarean section must be looked upon as a crippling operation from the point of view of future pregnancies. Many of these patients have only one baby. In 1,000 cases reported last year only sixty-four were delivered of their third or fourth babies. The sterilizing aspects of the operation, however, are not in conflict with the American norm of family size. With increasing

safety of the operation we are permitted greater latitude in the number of children that a woman may have before sterilization is carried out.

I also agree that the induction of labor, especially in medical complications such as toxemia, vascular disease, and diabetes, may become a competing procedure. We have been inducing labor in these cases with Pituitrin infusion and have been impressed with its value. It gives us a trial induction which does not compromise the later section if this becomes necessary. We will continue to explore the possibilities of this procedure with interest.

With reference to the decreased returns of the operation in terms of fetal salvage, I have been impressed with the fact that the economic law of diminishing returns applies to cesarean sections as Dr. Plass stated, but it varies for different indications. For placenta previa, the fetal salvage may increase as the section rate increases until a figure of near 90 per cent is reached, whereas, in breech presentation, the salvage rate does not improve to any extent after a section rate of 10 per cent. For the entire group, the top rate beyond which the fetal return is no longer appreciably increased is probably in the neighborhood of 6 per cent, varying with the type of service. This idea may be expressed in another way by saying that if we go beyond a certain ideal top cesarean section rate, the number of mothers that will require section to save one baby becomes too high.

Dr. Plass' disagreement with corrected fetal mortality rates which were used can be answered by saying that unless some correction is made it is difficult to say that the fetal samples are uniform. For example, if the lifesaving value of one operation is to be assessed against another, you start with a group of babies that is salvageable to begin with. I corrected the figures with the view that the lowest theoretical mortality rate could have been zero and any mortality above that measures the comparable failures of the procedures employed.

Dr. Schumann said that a 6 per cent incidence of cephalopelvic disproportion among the primiparas was too high; he does not believe there are that many cases with that indication. He is correct if he is talking about absolute degrees of disproportion, but we are dealing here with relative degrees of disproportion. Our concept of disproportion keeps on changing; it is not a static term. To justify the figure we can show that by raising the incidence of cesarean section for cephalopelvic disproportion from 2 to 6 per cent during the last fifteen years, we have reduced the midforceps rate by exactly the same margin. As a consequence, we have saved many more babies by doing the extra 4 per cent sections in these primiparas than we could have if we had delivered them by force through the vagina.

With every new advance in surgery which makes for greater safety to the mother, the variables involved in the concept of cephalopelvic disproportion need redefining. We have certainly progressed to the point where it is unjustified to attempt operative vaginal deliveries that will result in major trauma to either mother or baby. We are approaching this ideal of atraumatic obstetrics without losing mothers, by raising the incidence of cephalopelvic disproportion in our clinic to the figure that Dr. Schumann criticized.

Dr. Miller asked about our cases with fibroids. We do sections on 15 per cent of our total group that go through pregnancy with fibroids. This relatively small group of patients, therefore, is likely to have either very large or obstructing fibroids and as a consequence most of them were treated by hysterectomy.

## THE HISTOGENESIS OF UTERINE MYOMAS\*

OTTO H. SCHWARZ, M.D., AND SETH WISSNER, A.B., M.D., ST. LOUIS, MO.

*(From the Department of Obstetrics and Gynecology, Washington University  
School of Medicine)*

MANY years ago one of us (O. H. S.) studied a specimen of a uterus of a nulliparous 18-year-old girl, which showed very small myomas. Scattered throughout the wall were many small foci of growths which represented myomas in early stages. It was decided from the study of this uterus that these myomas originated from small arterioles and very small arteries. At that time, as now, it was generally believed that the most common origin of myomas was from adult cells or germ cells in the muscle fibers. This idea has been strongly supported by none less than the late Robert Meyer. Statements in the modern texts on gynecological pathology will state that this is an undecided question. We, therefore, thought it opportune to reinvestigate the entire subject.

From a review of all the literature it was found that the subject had been thoroughly studied by Robert Meyer<sup>6</sup> and Hans Albrecht.<sup>1</sup> In Meyer's review he discussed all the early theories concerning the cell origin and referred to several writers who considered an immature cell as the start of this development. Meyer dismissed this idea with the suggestion that the lesions arise from the normal uterine muscle, and substantiated this with an illustration showing the latter characteristics. He mentioned that blood vessels, especially the arteries, had been considered as a source of origin. He mentioned the work of Klebs, Roesger, Gottschalk, Stern and others. He stated that Aschoff, Faber, Willy, Becker, and himself felt that the smallest myomas did not have any relationship to the blood-vessel wall. Meyer also stated that Sakurai and Aschoff studied myomas 0.06 to 0.02 mm. in size, and found that they were not associated with the blood vessels. Capillaries appeared in those 0.2 mm. in size, but were regarded as secondary. There were no illustrations in Aschoff's work. We studied areas of this size, namely, 0.06 to 0.02 mm., and one cannot say for certain that these are going to be myomas. In these the relationship to the blood vessels can be demonstrated, but they are too small to be considered as initial lesions. Meyer mentioned that Stern, in seedling myomas 0.7 to 1 mm., found proliferation of muscle cells from the media; but says this is entirely contrary to most prevailing opinions. Albrecht, in a similar review, stated that no exact definite piece of work had been carried out which would settle the question of origin conclusively. He favors the origin from the uterine muscle and he points out that the uterine muscle cell has a great propensity for growth which is exemplified by its marked enlargement at full term in pregnancy. He feels that if this phenomenon is not frequently carried out a tendency could be developed in these muscle cells to produce myomas as a result of this prolonged resting period. To this point we shall refer later. Since 1930 the literature on the subject has been rather fragmentary

\*Presented at the Seventy-Second Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 16 to 18, 1949.

and articles that have some bearing on the point under discussion have appeared by Faulkner,<sup>2</sup> von Jasche, Horta, Homgren, Ravenna, Lipschütz.

Returning to the inactivity of uterine muscle cells as a possible factor in the development of myomas we would like to call attention here to the fact that during pregnancy the uterine circulation undergoes a much greater hyperplasia and hypertrophy comparatively than the muscle cells themselves. In the process of involution, the involution of the muscle cells is very nearly complete by six weeks and definitely so by eight. In the involution of the circulatory system, three to five months are required and unfortunately, very frequently, this is not complete, leaving certain old vestiges, giving rise to the condition known as chronic subinvolution, first accurately described by Fletcher Shaw. During pregnancy the increase in the caliber of the uterine vessels increases many fold as early as the sixteenth week, particularly at the placental site, continuing to enlarge until near the end of term. This stimulation can be directly attributed to the action of estrogens and progesterone, the two hormones acting together to bring about the final picture.



Fig. 1.—Nulliparous uterus; Age 18 years; supravaginal hysterectomy. Photograph slightly reduced. Uterus actually about 50 per cent enlarged. The walls are studded with small discrete myomas; the largest about 1 cm. in diameter is seen in the upper right side of the picture. The chief increase in size is due to very numerous foci of growths from microscopic size to 1 mm. throughout the entire uterus. (Specimen presented by Dr. E. Lee Dorsett, March, 1920.)

Many investigators have produced hyperplasia of the endometrium with estrogens alone. No attention, however, has been placed on the character of the uterine blood vessels under these conditions. It has been casually noted in the present study that in uterine walls in which there occurs a hyperplasia of the endometrium, particularly exhibiting the Swiss cheese pattern, invariably there is a marked hypertrophy and hyperplasia of uterine vessels in general, but particularly in the middle third of the uterine wall. This observation is being fur-

ther investigated and will be presented in detail in another paper in the very near future. Clinically, sterility has frequently been mentioned as a factor in the incidence of myomas. Cullen called attention to this quite strikingly in his monograph with Kelly in 1910. He points out that in his material about 50 per cent of the patients were sterile. Others had full-term pregnancies, but it is very striking that the number of pregnancies in these individuals was definitely limited to one or two. Further, if myomatous growths do not occur clinically by the age of 50 years they seldom develop. Also, if they are recognized after the menopause and are causing no symptoms and they are not removed, seldom do they show any great propensity of growth. Again, during pregnancy

Fig. 2.

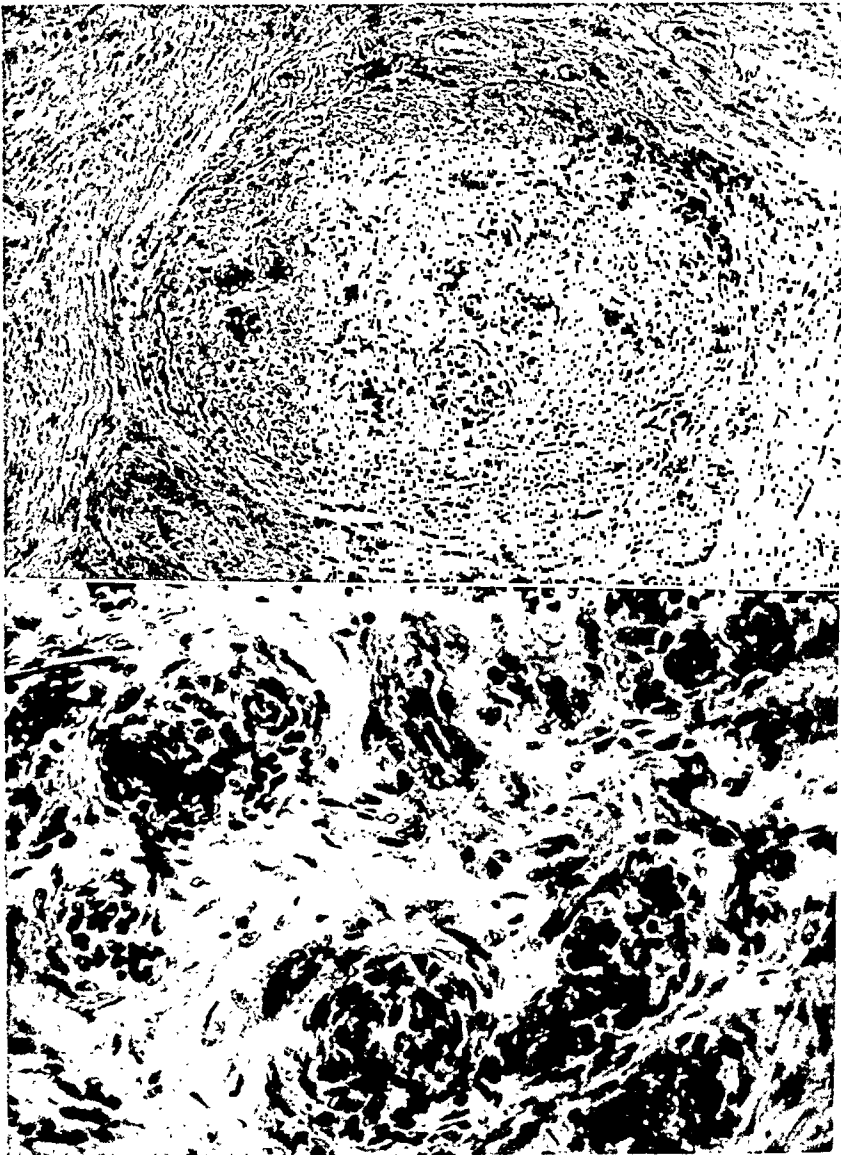


Fig. 3.

Fig. 2.—Section from Fig. 1. Shows a small very cellular myoma 0.4 mm. clearly encapsulated. The darker areas with cells in concentric arrangement have their origin from very small arteries. Myoma, 0.4 mm. in diameter.

Fig. 3.—High power of Fig. 2. Lumina of vessels in concentric areas readily compressed, but note the lumen is quite apparent in a slightly larger vessel in lower center of picture.

myomas seem to take on increased activity and even with this increased activity do not cause the patient any noticeable difficulties unless they undergo red degeneration, a type of degeneration which is seen at other times but more especially during pregnancy. If a woman delivers, having a myomatous uterus, it has been noted that these myomas will undergo involution as well as the uterus and it is stated by some that they actually disappear. This shrinking in size has also been noted from time to time in myomas which are recognized after the age of 50 years.

Fig. 4.

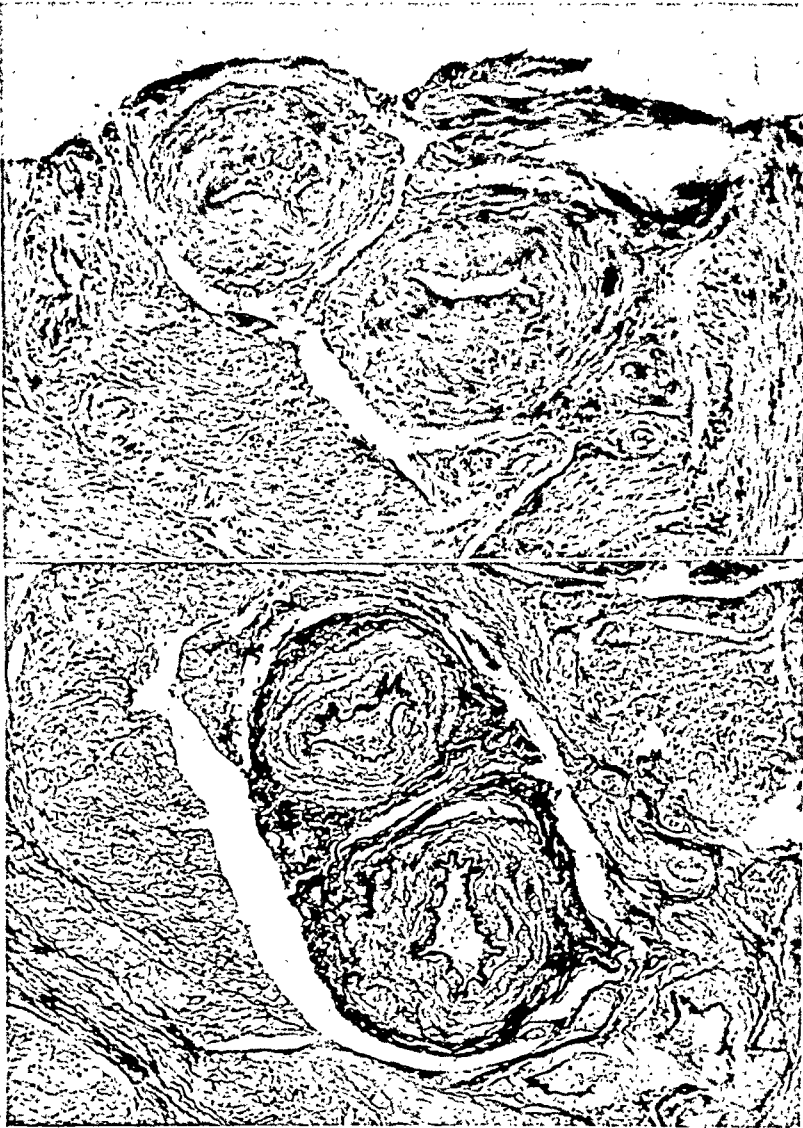


Fig. 5.

Fig. 4.—Normal arteries of good size, middle third of adult uterus. Note number of nuclei in media and compare with subsequent pictures of marked hyperplasia of vessels.

Fig. 5.—Same field as Fig. 4, orcein van Gieson stain. Elastic tissue stains dark brown, muscle, yellow, connective tissue, red. In black and white reproduction elastic tissue appears black, muscle light, connective tissue also black. Note normal internal elastic membrane, fine elastic tissue in light media, in outer periphery dark adventitia, which actually stains bright red in contrast.

TABLE VII. TABLE OF CLINICAL MATERIAL SHOWING DISTRIBUTION OF PATIENTS AND OBSTETRICAL FACTORS

Penicillin Series									
RACE	NUMBER OF CASES	SPONTANEOUS DELIVERIES	ELECTIVE LOW FORCEPS	OPERATIVE DELIVERIES	EPISIOTOMIES	COMPLICATIONS	TEMPERATURE		
							NORMAL	MORBIDITY*	
White	27	17	7	3	10	2 Prolonged ruptured membranes 1 Prolonged second stage 3 Second degree tears 1 Third degree tear	27	-	
Negro	27	17	6	4	8	a. Twins b. 1 Toxemia c. 2 Low cervical sections 1 Prolonged second stage 2 Second degree tears 1 Operative induction of labor 1 Tubal ligation 1 Uterine inertia	26	11	
Total	54	34	13	7	18	12	53	1	

\*Morbidity: Any case with a temperature of 100.4° F. on any two consecutive days.  
†Case 25 had uterine inertia for three days and prolonged ruptured membranes. Received penicillin 50,000 U. q.3.h. preoperatively. Had a low cervical section. Then penicillin in oil and wax 300,000 U. q.24.h. Temperature normal first day; second day 102° F.; third day 100° F.; fourth day 100° F.; then normal. Uterine culture sterile on third postpartum day. Etiology of temperature unknown, or operative reaction.

Series Without Penicillin*									
RACE	NUMBER OF CASES	SPONTANEOUS DELIVERIES	ELECTIVE LOW FORCEPS	OPERATIVE DELIVERIES	EPISIOTOMIES	COMPLICATIONS	TEMPERATURE		
							NORMAL	MORBIDITY	
White	4	3	1	-	1	1 Second degree tear	4	-	
Negro	28	24	2	2	4	1 Second degree tear 1 Upper respiratory infection 1 Infected episiotomy 1 Prolonged second stage	27	11	
Total	32	27	3	2	5	5	31	1	

\*Control series were taken from patients who had no temperature elevations in order that any possible infections would be excluded.  
†Case No. 47. Temperature rise etiology unknown.



are stimulated hormonally in a more selective manner. Another question that arises is, "Why do not myomas appear more frequently in experimental and certain domesticated animals?" It is well known that they occur and this subject is reviewed in the excellent monograph of Feldman. Our answer to that fact is that the life span of these animals is so short that it is not compatible with the growth of myomas which in the human being is also well known to be comparatively slow.



Fig. 8.—Large hypertrophied and hyperplastic artery. Note this type of hyperplasia produces a more fibrillated structure, such as is seen in many myomas. Note the proliferating media going into the adventitia, much like the extension of cells in a tissue culture.

### Material

We selected from our files sections of uterine walls as they appeared. These sections included the entire uterine wall from endometrium to peritoneum. Newer material was studied to the extent of about 100 uteri because we wished to stain the walls not only with hematoxylin and eosin but with orcein van Gieson stains. It had been the routine of our laboratories for a period of over seven years to stain the uterine wall with both stains, particularly to assist in making a diagnosis of so-called subinvolution. A total of some 750 specimens of the uterine wall were studied; more were available, but we feel sufficient evidence was gathered from this first series. In studying these sections we naturally looked for small foci of growth. Numerous small areas 1 mm. and less were found; a great many that measured between 2 mm. and 1 cm. were found as well. A certain number that were seen reached as high as 2 cm. in diameter.

In the early part of the study we soon found out that it was far less difficult to determine whether an early myomatous development came from the media of vessels, especially the arteries, than from the muscle per se. We feel our illustrations will bear out this point and, therefore, without going into any great detail concerning our findings, we felt it would clarify matters to give rather detailed legends with each illustration. In myomas which we felt came from very small vessels the structure was rather consistent. Such lesions developed into very cellular myomas; the cells showed thickened and blunt-end nuclei with comparatively little cytoplasm. In these lesions numerous

A question which is immediately asked when one attempts to emphasize the uterine blood vessel origin is, "Why do not myomas grow in the media of blood vessels in general?" They actually do, but only on rare occasions. Outside of the uterine body there are very few blood vessels which are not carrying out their almost full physiological function constantly. The vessels in the kidneys may be a slight exception because no doubt during pregnancy an increased volume of blood flows through them as has been shown experimentally. The ovarian vessels, of course, are almost continually in a state of hyperplastic activity and retrogression. Apparently, both the uterine and ovarian vessels

Fig. 6.



Fig. 7.

Fig. 6.—Shows two small arteries (hematoxylin and eosin stain). Both have same size lumen. Upper one shows marked proliferation in myoma-like fashion, lower presents no special activity.

Fig. 7.—Same field as Fig. 6. Orcein van Gieson stain. Note internal elastic membranes both same size, upper and lower compressed but similar in size; this is the smaller vessel in Fig. 6.

the blood supply must come from the existing vasa vasorum which in turn must undergo hyperplasia if sufficient nutrition is to be supplied. This point is emphasized by the fact that even in small masses of this kind (1 or 2 mm. in diameter) the center of these areas occasionally shows some early hyalinization. One such case is clearly demonstrated in our illustrations (Fig. 11).

There is a third pattern of myoma which we have seen in the series as well, and these are more or less encapsulated masses which we feel come from the walls of fair-sized veins. Larger myomas with this pattern are also encountered. We

Fig. 11.



Fig. 12.

Fig. 11.—Encapsulated mass of myomatous tissue 0.6 mm. showing thin spindled type of cell, characteristic of the cells seen in markedly hyperplastic uterine vessels. Origin from large artery, note the beginning hyalinization in the center. Nutrition of such lesions must be taken up by hypertrophic vasa vasorum; if this is not sufficient, early hyalinization occurs. This is entirely different from the small artery development which takes care of itself as growth continues.

Fig. 12.—Orcein van Gieson stain, same field as Fig. 11, proving it to be an artery involved. Reduplication of internal elastic membrane indicates multiparity (chronic subinvolution), but note how elastic membranes are broken up and diffused as seen in Fig. 13.

foci herded themselves together to form small encapsulated nodules. These myomas in developing actually received their nutrition from the vessels which formed them. Hypertrophy and hyperplasia of the larger vessels, especially those of the middle third, were common findings. This picture was controlled by the fact that in certain uteri the vessels for their size appeared as would other vessels in any other part of the body. The hyperplasia was particularly conspicuous in the larger arteries and veins, and there a different type of structure developed. This consisted chiefly of many elongated deeply staining nuclei running more or less in a fibrillated manner. The periphery of the vessel was involved first, then its center was involved, and finally the original lumen of the large vessels was obliterated. In order that these masses can continue to grow,

Fig. 9.



Fig. 10.

Fig. 9.—A very cellular circumscribed clearly demarcated structure made up of hyperplastic muscle cells 0.6 mm. in diameter, very fibrillar in type. Note the center opening of vessel filled with blood.

Fig. 10.—Orcein van Gieson stain, same field as Fig. 9. Note the almost complete destruction of the internal elastic membrane with the diffusion of elastic tissue chiefly to the right. This is not comparable to changes in chronic subinvolution (see text).

these small myomas show a very marked proliferation of their media made up entirely of deep-staining, closely packed cells with a tendency to invade the neighboring matrix. It would seem that this might be considered under these circumstances as the source of their original development.

In studying areas associated with large arteries the media shows marked proliferation. A good-sized internal elastic membrane in varying stages of disintegration can be demonstrated. The internal elastic membrane is broken by the activity or pressure of these cells and can be demonstrated as present in the wall of such an artery in a diffused state (Fig. 10). The character of this lesion is not to be confused in any way with the abnormal distribution of the elastic tissue in the picture of subinvolution of the arteries.

Fig. 15.

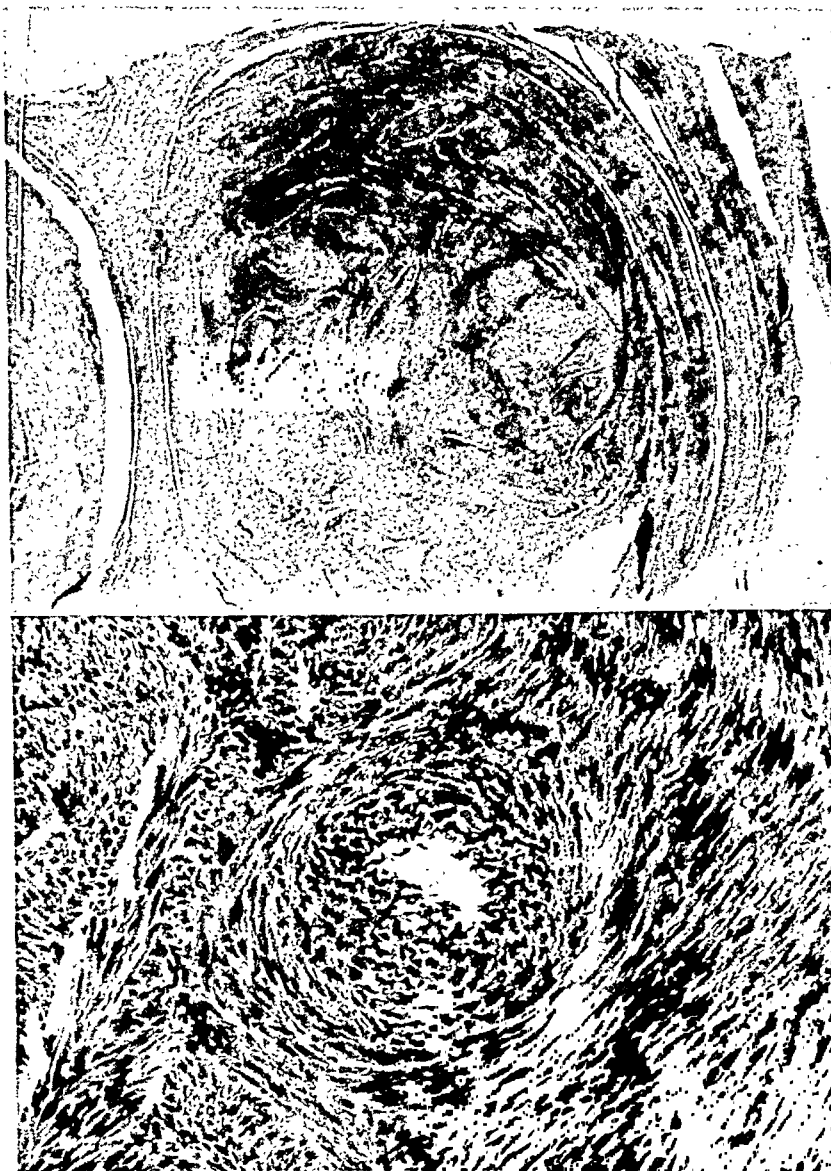


Fig. 16.

Fig. 15.—Low power, encapsulated intramural myoma, 8 mm. in diameter, rich in small arteries, which are hypertrophied, a lesser number of veins visible.

Fig. 16.—High power of Fig. 15. Single artery, markedly hypertrophied, with striking increase in hypertrophied cells. Note the concentric pattern in the periphery of the vessels. No adventitia.

have illustrated two (Figs. 13 and 14). The search for lesions developing from the muscle fibers themselves was diligently carried out. Many suggestive patterns were seen, but we state emphatically that it is far easier to find evidence of these early lesions coming from blood vessels than from the muscle tissue itself. Of course, when the myoma develops to any size greater than 2 cm. it is almost impossible to make any definite assertions as to origin, with one exception. We have noted in myomas from 2 mm. to 1 cm. in diameter that they contain many arteries and veins, but the veins are not readily distinguishable. Perhaps the reason is that the veins are more readily compressed, and their walls intimately incorporated in the substance of the growing tissue. Frequently the vessels in

Fig. 13.

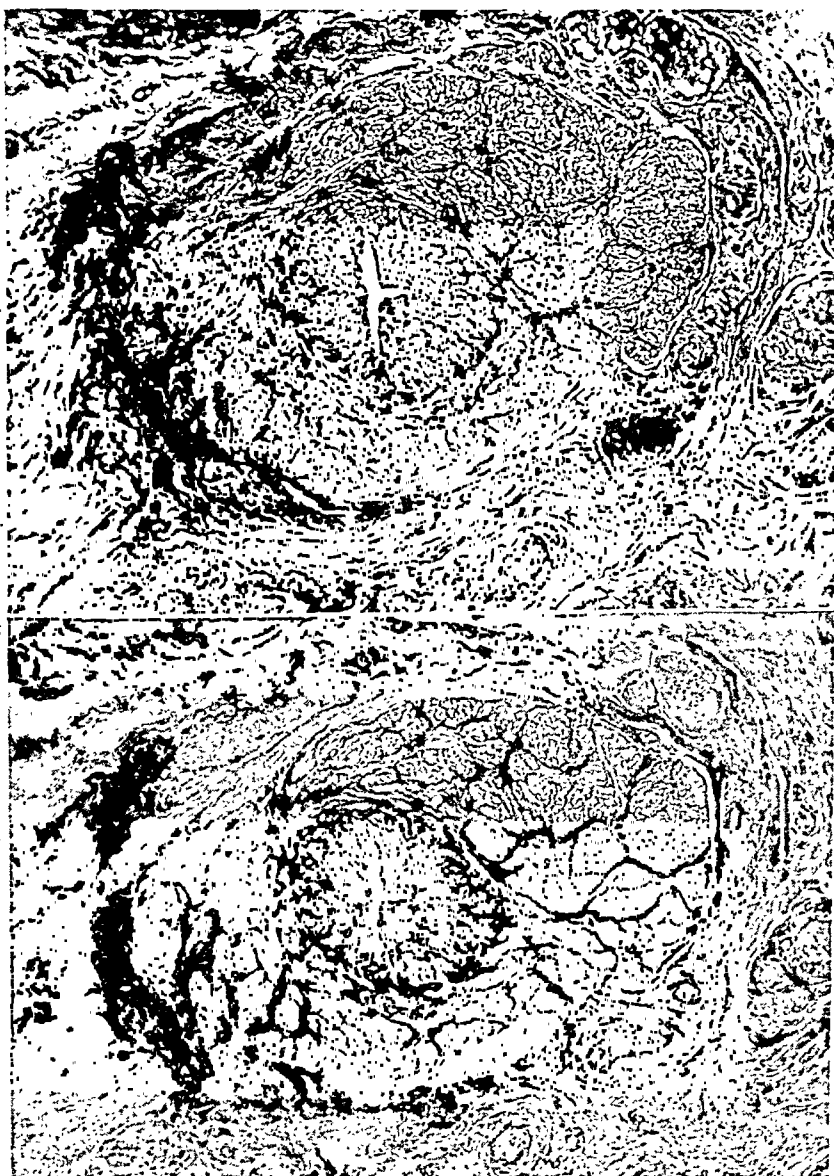


Fig. 14.

Fig. 13.—Circumscribed nodule 0.4 mm. of myomatous tissue, pattern of which is sometimes seen in larger myomas—center lumen of a vein, muscle bundles in vascular form; sprinkling of large muscle cells throughout area; marked cellular activity in walls of tiny arteries in area immediately surrounding mass.

Fig. 14.—Same area as Fig. 13. Orcein van Gieson stain. Note circle of irregular elastic tissue at the periphery of original vein (sometimes referred to as "the external elastic membrane" in vein). This diffuses into the original thin wall as well as into the surrounding hypertrophied area.

veins do not penetrate the tumor. Histological study of a tumor, however, should not be relied upon too much for identification of vessels because it is generally taught that young, and even older, blood vessels of either series in a growing tumor, may all look alike. It is to be pointed out that veins are easily injectable in the trabeculae of a compound myoma, and on the other hand in adenomyoma, which is usually under no great tension within its contained space, veins again fail to inject as in the ordinary myoma. Furthermore, in a tumor which has been the victim of such a serious obstructive vascular accident as acute red degeneration, dilated lymphatic spaces should be and are present, and complicate the problem of positive identification.

DR. EMIL NOVAK, Baltimore, Md.—Dr. Schwarz, in the presentation of his paper, initiated a method of presentation which might well be emulated: State your conclusions first, and then try to prove them with your slides. The orcein-van Gieson technique which Dr. Schwarz has so effectively employed since his early days of study in the German laboratories has stood him in good stead in the present investigation. As I watched his slides, however, I had the distinct feeling that they threw much more light on the behavior of blood-vessels within myomas than they did on the histogenesis of these tumors. The thickening of the muscularis seen in many of the blood vessels was often localized, giving one the impression that the picture was due simply to tangential section, much as we see in the study of blood vessels elsewhere, especially when the course of the vessels is not straight but more or less curved or spiral. I am glad that Dr. Schwarz did not inject the endocrine factor in his discussion of the origin of myomas, for the evidence for this is pretty slim. The question of whether these tumors have their source in certain rather immature cells of the uterine musculature, or from the muscularis of the blood vessels, is still an open one, but Dr. Schwarz's study has been a provocative one, and his conclusions have been very conservative.

DR. SCHWARZ (Closing).—I did not mention in the paper the physiologic hyperplastic changes in the normal uterus during pregnancy, for example. First of all I want to say something about the adenomyosis case which Dr. Faulkner injected and which showed no veins. Any one can take an ordinary section of a normal uterine wall and notice that the arteries are outstanding but you will have to look more carefully for the veins. This is illustrated as well in the pregnant uterus. The veins develop along with the arteries and you see them as outstanding accompaniments whereas in the ordinary uterine wall the veins are compressed and not so conspicuous histologically as are the arteries.

Also, I did not discuss the endocrine problem, but I believe that in the origin of myomas there is some abnormal stimulation of estrogen and progesterone. In that connection I can cite a case of a uterus of a woman aged seventy-eight years. She had received estrogen and progesterone for the past two years by Masters of St. Louis, who is making special observations on the effect of estrogens and progesterone on the aged. These slides show hyalinization present very strikingly at this advanced age and throughout there is proliferation of new cells in the media of the vessels.

## Conclusions

We conclude from the study of our material that myomas commonly arise from small arterioles containing smooth muscle in their walls, small and large arteries, and from both large and small veins. We feel that it is much more difficult to show evidence that they actually arise from muscle bundles; and although we made considerable effort to demonstrate lesions suggestive of this origin, we found none impressive enough for illustration. The very close relationship in most instances of small myomatous areas to the blood vessels, and, on the other hand, their actual development from the blood vessels, make it very difficult to account for muscle-fiber cell origin, because of the difficulty in determining landmarks, which one can readily do in the case of the blood vessels. We found that the illustrations in the literature were meager, mostly not clear, and almost no photographs were found; consequently we feel that no clear-cut illustrations have been presented to date. We do not question the fact that muscle-fiber origin may occur as many careful observers have concluded, but we question very much that the uterine muscle fiber per se plays any great part in the development of myomas. We acknowledge that this origin may exist, but we feel that the blood vessel origin is the more common.

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## Discussion

DR. ROBERT L. FAULKNER, Cleveland, Ohio.—Positive determination of the origin of a common tumor such as uterine myoma would be a landmark in gynecology. Dr. Schwarz presents evidence that myomas, more frequently than is usually thought, originate from blood vessels, particularly arteries. From the mere nature of the growth of myomas, there may arise doubt that this matter is irrevocably settled and I am sure the author himself has no such idea.

Many years ago, John Sampson spoke of the "basket" pattern of arteries surrounding the young myoma with branches here and there penetrating its substance and furnishing its nourishment. The impression of probable function gained from such a pattern is that the vessels are called into being to feed a parasitic body suddenly arising in their midst.

As myomas enlarge even slightly, most of them, not all, become veritable masses of blood vessels which inject as arteries, and here it seems to me is the crux of the situation in interpreting proliferative changes in vessels. Since there is and has to be amazing growth of blood vessels within the tumor to keep pace with its increasing size, the interpretation of proliferative cellular changes within the vessels themselves has to be made with the question in mind as to whether the activity represents tumor growth toward the usual nonangiomatous myoma kind, or is simply reproduction of themselves as blood vessels.

The author has definite ideas as to why veins do not inject in myomas, and he may be right that compression is a factor in producing failure of injection, rather than that



The selection of the cases for operation was made without in any way altering the preoperative test as originally described. The primary complaint in every instance was urinary stress incontinence. With but a single exception, all of the patients had borne one or more children. Four of them had had vaginal repairs of the Manchester type with plication of the vesical sphincter. Another four had a urethrocele combined with a slight to moderate cystocele. Two were elderly women (aged 60 and 75 years) totally incontinent without any degree of prolapse and with only a small degree of anterior vaginal wall relaxation. One had no clinical evidence of any loss of support of the urethra or of the vagina. The last or twelfth patient was of special interest. She had had a total hysterectomy for a submucous myoma and at the same time a vesicourethral suspension for exertional incontinence. Ten weeks later the loss of urinary control recurred and became progressively worse. She was recently subjected to a second suspension operation. This case presented the opportunity to search for the cause of the failure of the first operation and will be referred to later.

A few steps in the technique of the operation have been altered in this group, but not radically. In the original description, the first series of sutures placed laterally and equidistant along the course of the urethra between the external meatus and the vesical neck was made to include a portion of the wall of the urethra as well as the wall of the vagina. Now these sutures are directed to exclude the urethra and to include a stout bite of the vaginal wall adjacent to the urethra. This change should avoid the risk of urethral damage. Although hematuria and the formation of a fistula were never problems complicating the initial series of cases, eliminating the hazard of injury to the urethra by placing the sutures solely in the vaginal wall should lend more security to their grasp. Instead of allowing the Foley catheter to remain in the bladder for several days, it is now removed immediately after operation. On seven more recent occasions, the suprapubic wound was closed without drainage.

As part of the study, cystometry and cystography before and after operation were used as additional sources of information.

The cystometric determinations showed a comparably normal detrusor mechanism in every instance. No change was noted that could be associated solely with stress incontinence or the correction of it. The importance and usefulness of cystometry in the differential diagnosis of conditions causing increased intravesical pressure or a neurogenic bladder are appreciated.

The cystogram was the source of more positive information. A total of seventy-five cystographic observations were made on eight of the patients with incontinence and on five continent women used as controls. From 200 to 250 c.c. of 5 per cent sodium iodide were instilled into the bladder for cystography. Films were taken before and after operation with the patients in the recumbent and erect positions, and also while voiding in the standing position.

In the continent woman while she is recumbent, the outline of the base of the bladder lies just at or little above the symphysis pubis (Fig. 1, A). When she stands erect, the position of the bladder is maintained (Fig. 2, A). A voluntary attempt at micturition transforms the base of the bladder to a funnel-

## THE FEMALE BLADDER AND URETHRA BEFORE AND AFTER CORRECTION FOR STRESS INCONTINENCE\*

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ON JUNE 8, 1944, approximately five years ago, simple vesicourethral suspension by the suprapubic route as described by Marshall and his co-workers<sup>1</sup> was first tried for the correction of female urinary stress incontinence. Their experience with the procedure from that day to May 11, 1948, a period of almost four years, was just recently published.<sup>1</sup> That report includes the story of how the idea was conceived, the description of a preoperative test designed to make the selection of candidates for the operation most suitable, the description of the technique of the operation itself, and an analysis of the results of the operation. No formal attempt was made by the authors to explain or evaluate the mechanics by which that particular operation restores or improves urinary control.

Fifty patients constituted the basis of their clinical analysis, thirty-eight of whom were women operated upon specifically for urinary stress incontinence. Of this latter group, it is noteworthy that twenty-five, or two-thirds of them, had had a total of forty standard operations which routinely should relieve urinary control, but had failed in these cases. After simple vesicourethral suspension was performed upon the thirty-eight women with stress incontinence, the incidence of complete failures was 8 per cent. In 74 per cent of the same group the result was entirely satisfactory and in 18 per cent was considered definitely improved. Wilfred Shaw<sup>2</sup> makes the comment that "vaginal operations for the relief of stress incontinence have one factor in common—the originators always claim good results." The approach by Marshall and his co-workers is not per vaginam. The claim, however, runs true. In fact, as our experience enlarges, it may be found that simple vesicourethral suspension by the suprapubic route may yield better results than some of the commonly used vaginal operations. Its worthiest indication as the procedure of choice is in cases of recurring incontinence where repeated vaginal operations have failed and have produced so much scar tissue that further attempts through the same route would be almost impossible.

For the past eighteen months, the author's experience and observations with this procedure have expanded by intensively studying twelve additional patients with the complaint of exertional incontinence. Interest and attention were focused on the disclosure of factors contributing to and explaining the mechanism of the procedure's success. It is the purpose of this communication to present an evaluation of the clinical and anatomical findings that were further accumulated before and after operation in the course of this study.

\*Presented, by invitation, at the Seventy-Second Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 16 to 18, 1949.

having four vaginal examinations and whose labor was operatively induced. The third patient had received 100,000 units of penicillin every 12 hours, and the culture yielded penicillin-resistant *Escherichia coli*. She was a 21-year-old white woman with no living children, whose only complication was a third degree perineal laceration.

Four of the 14 positive cultures were taken over 72 hours after delivery. Two of these patients received a single injection of 200,000 units of penicillin on admission and the same amount one hour post partum. These cases yielded *Gaffkya*, anaerobic diphtheroides, anaerobic streptococci and pleuropneumonia-like organisms. The other two patients received only a single injection of 200,000 units of penicillin on admission and showed anaerobic streptococci from one case and *E. coli* from the other. All of these patients delivered without untoward incident. Case No. 95, which yielded *E. coli*, was a patient who had a Pomeroy sterilization post partum for grand multiparity.

As shown in Table VII, there was only one case in the penicillin series that had a temperature elevation of 100.4° F. or more on any two days post partum. This patient had uterine inertia for three days and prolonged ruptured membranes. She was placed on penicillin, 50,000 units every 3 hours, 24 hours after the membranes ruptured, and therapy was continued until the time of operation. She was delivered by a low cervical cesarean section and was placed on penicillin in oil and wax, 300,000 units daily. Her temperature on the second postoperative day was 102° F., the third day 100.4° F., the fourth day 100° F., and thereafter her temperature was normal. The uterine culture taken on the third postoperative day was sterile. No cause for the temperature elevation could be found.

The morbidity in the two series of patients is not comparable, since the patients in the control series were selected on the basis of a normal temperature, as mentioned before, whereas patients in the penicillin series were selected at random when they reached the delivery floor, and were followed regardless of their complications. However, it seems to us that the low morbidity in the penicillin series may be significant, although the series is obviously too small to be conclusive.

### Discussion

Even though this study is open to criticism because of the limited number of cases involved, we think that we are justified in reporting the results at this time because they seem sufficiently convincing. The incidence of sterile cultures in the penicillin series as contrasted with the control series, 59.4 per cent as against 6.2 per cent, is certainly significant. If we may discount the presence of the penicillin-resistant, probably nonpathogenic pleuropneumonia-like organisms, then the number of cultures showing no significant organisms in the penicillin-treated cases is 74.1 per cent. As shown in Tables I and II, the predominating organisms in the control series were penicillin-sensitive anaerobic streptococci and *Bacteroides*, both of which were markedly decreased in the penicillin series (Table III). As shown in Table IV, from only one patient receiving larger doses of penicillin was a penicillin-sensitive anaerobic streptococcus isolated, the only other organisms occurring in such cases being penicillin-resistant *A. aerogenes* and *E. coli*, and a probably nonpathogenic diphtheroid. All but one of the cases in the penicillin series which showed penicillin-sensitive *Bacteroides* and anaerobic streptococci were those on low penicillin dosages and those in which cultures were taken later than 48 hours after delivery. This would seem to indicate that relatively high dosages of penicillin, given prepartum and postpartum, may eliminate penicillin-sensitive organisms from the uterus for at least three days or more post partum, and that a small amount given early in labor may be effective up to 48 hours following delivery.

shaped structure and shows some descent of the vesical neck (Fig. 1, *B*). As micturition is initiated, the effect of the detrusor mechanism is noted in the change of the shape of the bladder and in the "funneling" and descent of the vesical neck (Fig. 2, *B*). It should be stated that the subjects used as controls were nulliparous and parous women with normal urinary control and well-supported vaginas.

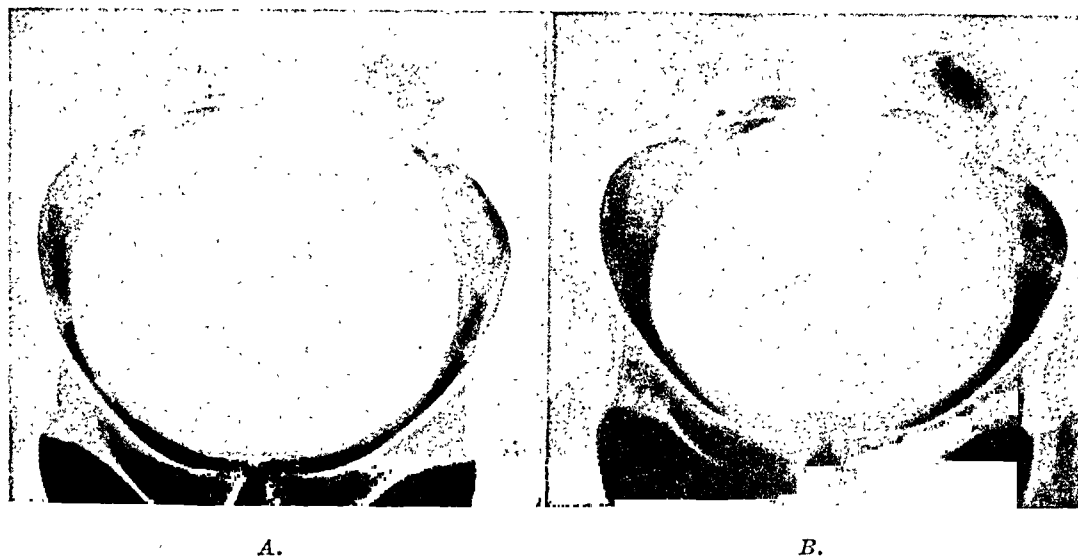


Fig. 1.—M. R. (GH No. 9477). Multipara, continent. *A*, Recumbent position. Outline of base of bladder a little above superior edge of symphysis. In the erect position, the same relationship is noted. *B*, Voluntary attempt at micturition in erect position. Note funnel shape and descent of base and neck of bladder.

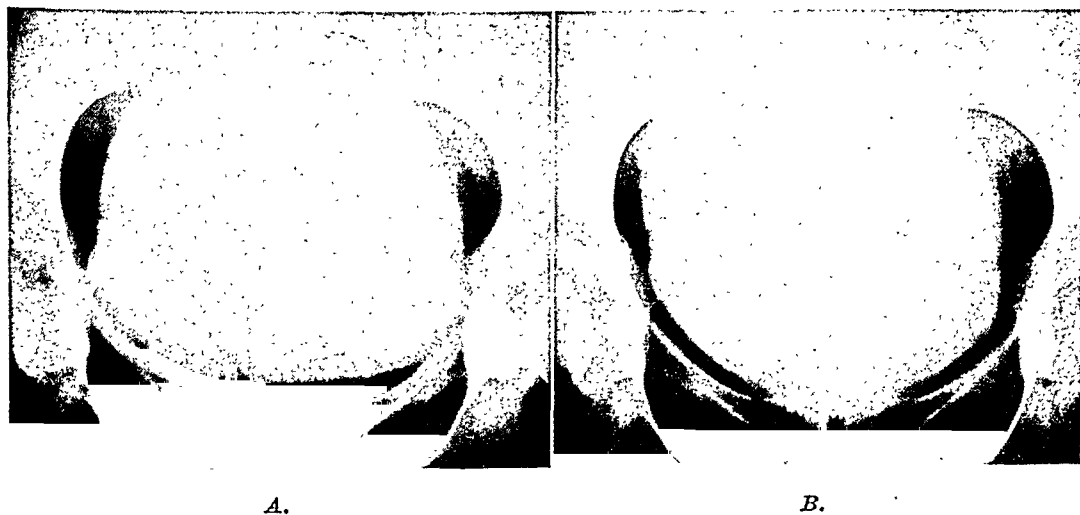


Fig. 2.—E. E. (GH No. 6146). Nullipara, continent. *A*, Erect position. Level of base of bladder just above symphysis. Same relationship observed with patient in recumbent position. *B*, Act of micturition initiated. Note funnel shape and descent of base and neck of bladder.

In seven of the patients with stress incontinence, the findings as revealed by cystography before operation were essentially uniform. In the recumbent position, the base of the bladder is well below the superior border of the symphysis (Figs. 3, *A* and 4, *A*). In the erect position, the bladder descends a little lower with the base and neck assuming the shape of a funnel (Figs. 3, *B* and 4, *B*). These observations indicate that there must be some weakness or relaxation predominantly of the supportive structures of the pelvic floor, or of the internal vesical sphincter mechanism, or both.

The exception to these regular findings was noted in the eighth patient with stress incontinence of moderate degree and without any clinical evidence of loss of vaginal support. Both in the recumbent and standing positions, the cystograms failed to demonstrate the characteristic shadows of the incontinent bladder, in fact, they were not unlike those of the continent woman (Figs. 5, *A* and 5, *B*). This situation, in the absence of other demonstrable causes, points to an incompetent vesical sphincter not associated with inadequate vaginal support.

*A.**B.**C.**D.*

Fig. 3.—C. Y. (GH No. 16755), aged 51 years. Nullipara, stress incontinence with moderate urethrocystocele. *A*, Recumbent position before operation. Base and neck of bladder well below superior border of symphysis. *B*, Erect position before operation. Note descent and "funneling" of vesical outlet. *C*, Recumbent position after operation. *D*, Erect position after operation. Note degree of elevation of bladder.

In general, these observations on the continent and incontinent bladder are in agreement with those just recently published by Muellner.<sup>3</sup> His study on the etiology of stress incontinence based on many fluoroscopic observations not only comprises illustrations of the position of the bladder and vesical neck in subjects who have normal urinary control and in those who are incontinent, but also demonstrates the mechanics of micturition in both.

Following suprapubic vesicourethral suspension, the most striking observation made by cystography is the degree of elevation of the bladder that is effected by the operations (Figs. 3, *C*, 3, *D*, 3, *E*, 4, *C*, 4, *D*, 5, *C*, 5, *D* and 5, *E*). Although urinary control has been restored in all of these patients to date, it is noted that the position of the base of the bladder is slightly lower in the erect posture when compared to the recumbent (compare Figs. 3, *C*, 4, *C*, 5, *C* to

Figs. 3, *D*, 4, *D*, 5, *D*). Some of the distortion that is noted of the vesical shadows postoperatively are inevitably the result of the manner in which the structures were fixed to the symphysis and the adjacent tissues. It is observed that the bladder neck and the urethra are closely approximated to the superior surface of the symphysis pubis without showing any distortion of their contour and lumen (Fig. 6).

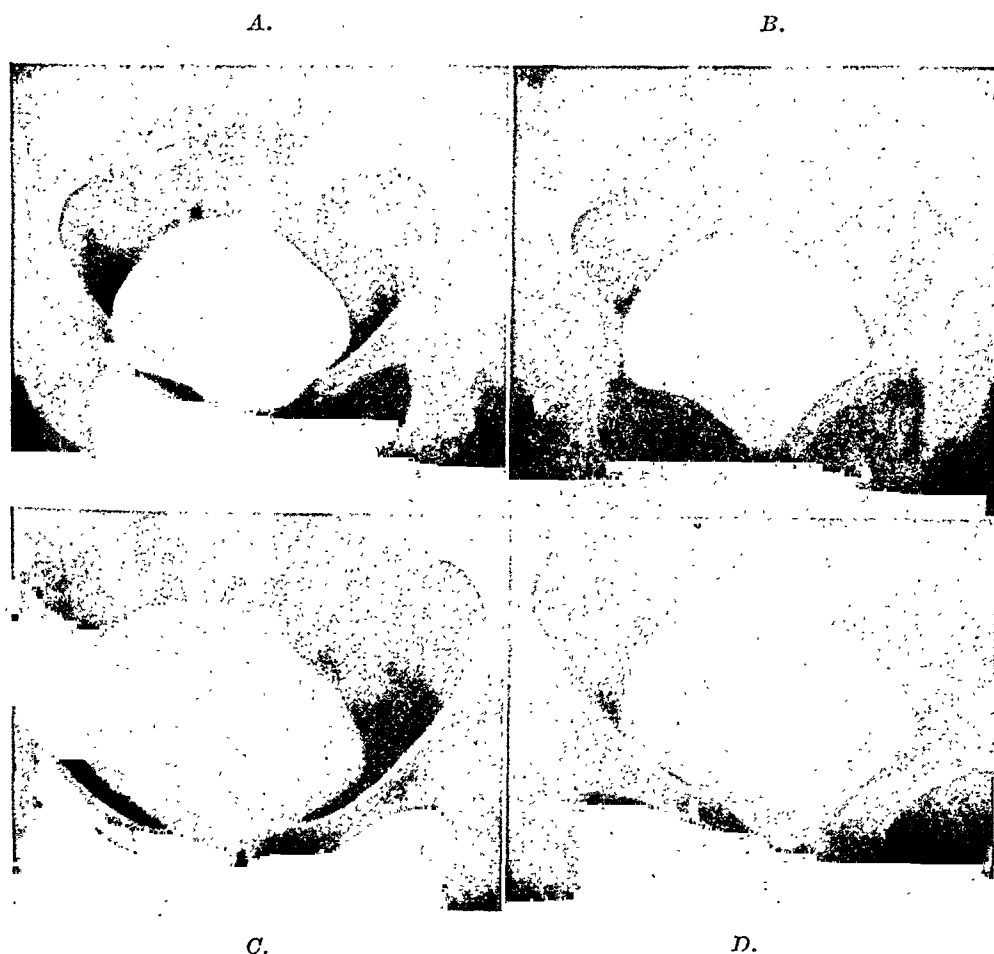


Fig. 4.—E. C. (GH. No. 12662), aged 60 years, para iii. Recurring stress incontinence after Manchester type of repair and plication of vesical sphincter. *A*, Recumbent position. *B*, Erect position before operation. Level of base and neck of bladder well below superior border of symphysis. *C*, Recumbent position. *D*, Erect position after operation. Note degree of elevation.

Two clinical histories should be briefly reviewed at this point. First, the case that required a second vesicourethral suspension.

CASE 1.—T. L. (WRH, No. 279499), para iii, aged 39 years, had a total hysterectomy for a submucous myoma and a suprapubic vesicourethral suspension for stress incontinence on July 29, 1948. During October of the same year the incontinence recurred and became progressively worse. The author was called in consultation early in April of this year. By vaginal examination the urethra appeared to be well suspended. Stress incontinence, however, could be readily demonstrated. The preoperative test indicated that she was eligible for a second operation. On April 22, 1949, the author personally explored the site of the former operation and it was found that most of the urethra was well fixed and densely adherent to the posterior surface of the symphysis, but that the vesical neck and base of the bladder were relaxed and unsupported. The suspension and fixation of these structures were accomplished accordingly. The patient was discharged from the hospital in due time with a satisfactory recovery.

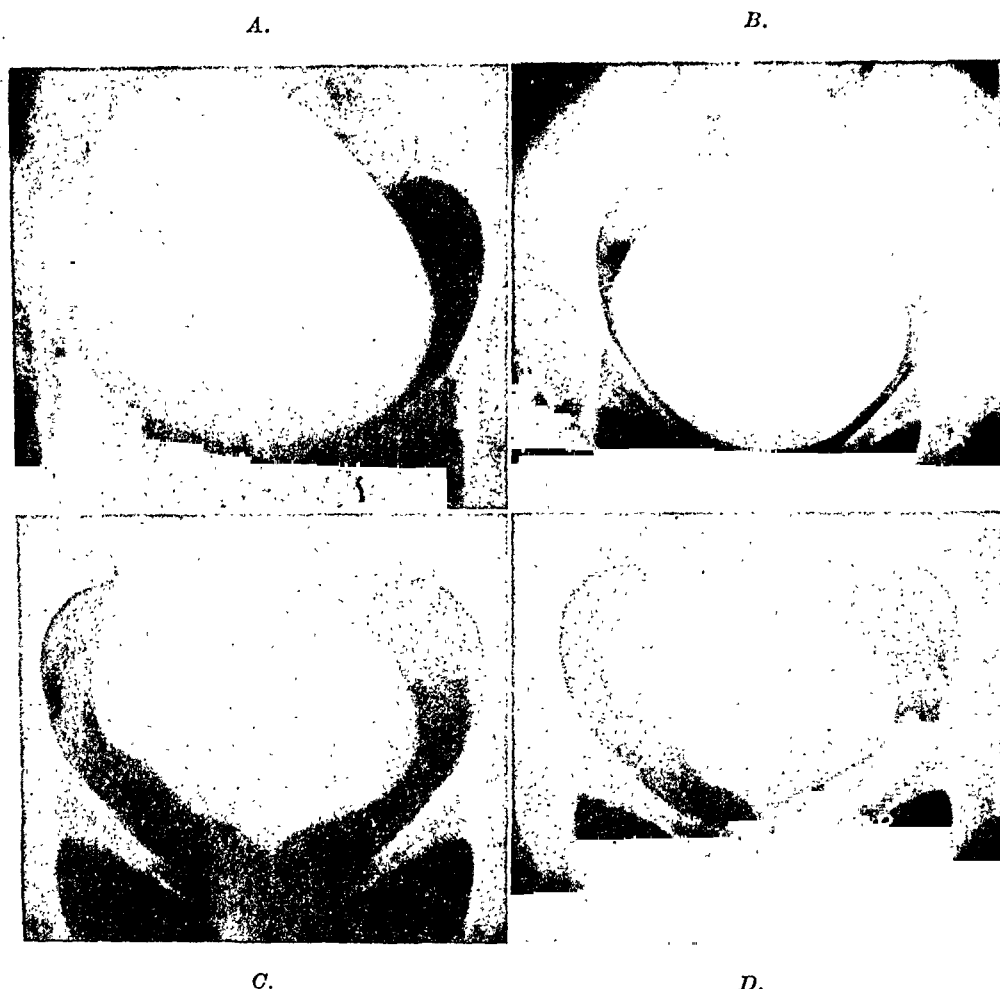
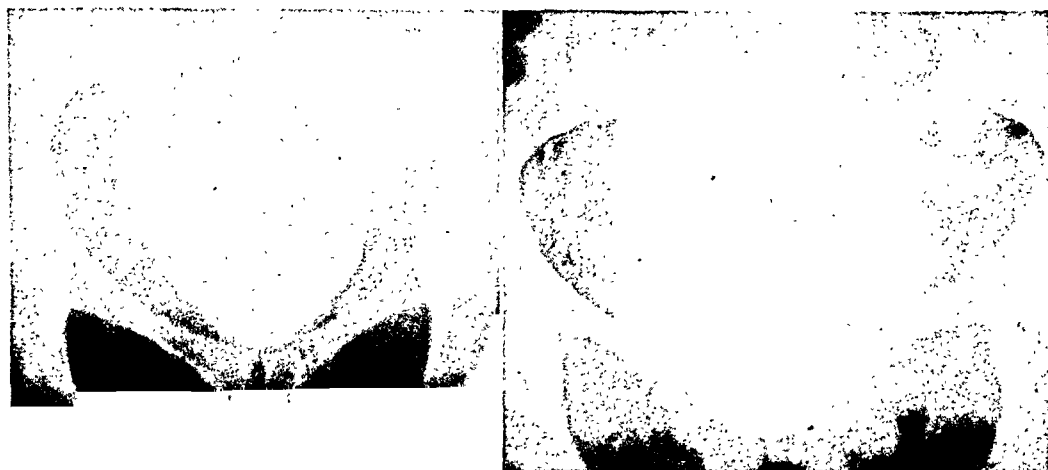


Fig. 5.—E. H. (GH No. 17692), aged 44 years, para iv. Stress incontinence without any clinical evidence of loss of support. *A*, Recumbent position. *B*, Erect position before operation. Note lack of descent of bladder. Findings simulate those observed in normally continent woman. *C*, Recumbent position. *D*, Erect position after operation. Degree of elevation of bladder is notable.



Figs. 3E and 5E.—Position of bladder during micturition after operation.

It was revealed by the former operator, who was attempting the procedure for the first time when he did the operation in July, 1948, that he had employed only six sutures to fix the urethra to the symphysis, and had failed to suspend the vesical outlet and base. If in this patient's follow-up she remains continent, the reason for the failure following the first operation is obvious.



Fig. 6.—B. B. (GH No. 8482), aged 34 years. After operation for stress incontinence. Half lateral view showing close approximation of urethra to posterior surface of symphysis. No distortion of urethra is in evidence.

The second case came under observation at the Gallinger Municipal Hospital.

CASE 2.—F. W. (GMH No. D271), para viii, aged 36 years, was admitted Aug. 8, 1948, complaining of urinary stress incontinence. She had a second-degree urethrocystocele. Her last menstrual period began July 13, 1948. A suprapubic vesicourethral suspension was performed on August 12. No menstrual period appeared in August and shortly thereafter the diagnosis of pregnancy was established. Throughout pregnancy good urinary control was maintained. The disposition of the case when she would reach term was repeatedly discussed and cesarean section was considered. On March 3, 1949, approximately six weeks before the estimated date of confinement, she was admitted to the delivery suite with ruptured membranes, the vertex deeply engaged, and after a labor of two hours and fifteen minutes with the aid of a midline episiotomy was delivered spontaneously of an infant weighing 5 pounds, 5 ounces. To date she has retained good urinary control.

This case is unique in the sense that it is the first record of a pregnancy and delivery, albeit premature, occurring soon after this type of operation. It raises the question whether cesarean section will be found necessary under such circumstances, inasmuch as the location where the defect is corrected is at the outer periphery of the birth canal and fixed to a position where trauma from overstretching is less likely.

### Comment

However controversial are the reasons advanced to explain the causes of female urinary stress incontinence, it seems fairly established that the strategic factor in the restoration of urinary control lies in the rehabilitation of the vesical sphincter mechanism located in the bladder neck and the upper third of the urethra. Failure of the pelvic floor, especially the levator ani, to support the vesical neck, weakness or relaxation of the internal sphincter mechanism



of the urethra, any separation of the normal anatomical attachments of the vesical sphincter mechanism may result in stress incontinence. Whether these defects are caused by trauma associated with childbirth and obstetrical procedures, by congenital weakness, or by changes associated with senility, it is the vesical sphincter mechanism that occupies the center of the stage. Kelly<sup>4</sup> aptly states that "the key to successful treatment lies at the internal orifice of the urethra and in the sphincter muscle which controls the canal at this point." The case that required a second vesicourethral suspension adequately illustrates why the first one might have failed. The key to successful treatment, that is to say, the importance that should have been given to the elevation and fixation of the bladder neck, was overlooked.

It is known that stress incontinence may develop in the absence of any clinical evidence of the loss of the supporting structures in the pelvic floor, just as it is known that urinary control may be maintained in the presence of some relaxation. An evaluation of the cystographic findings that were observed in this study gives evidence that relaxation of the structures supporting the bladder neck is most frequently associated with stress incontinence.

Without excluding the usefulness and the indications of other operations that have long been tried and found successful, further evaluation of the experience that has been gained from the use of suprapubic vesicourethral suspension for the correction of stress incontinence presents the following points of advantage. The approach is simple and the technique is not difficult. The field of operation is relatively roomy and permits of a full view of the superior and lateral aspects of the urethra, the all-important neck of the bladder, and the base of the bladder. The procedure may follow a laparotomy in cases where combined vaginal surgery may not be indicated, but the need for the correction of exertional incontinence is present. It may be elected among elderly patients in whom a major vaginal operation is not advisable, but the restoration of urinary control is paramount for their comfort and well-being. It may be further elected in women, particularly those in the childbearing age, who complain solely of stress incontinence and who appear to have no need for vaginal plastic surgery. It is especially an advantageous procedure in cases of recurring loss of urinary control where repeated standard vaginal operations have failed.

The postoperative cystographic observations demonstrate that the most evident change effected by the procedure is the elevation of the bladder and the vesical outlet, and the fixation of the urethra without distorting it to the posterior surface of the symphysis pubis.

Since no muscles are plicated and no hammocklike support is constructed under the internal sphincter, it appears that the mechanism by which simple vesicourethral suspension restores or improves urinary control is as it was implied in the analysis of the original series. Most sphincters have two or more relatively firm attachments for the execution of their normal function. Simple elevation and fixation of the vesical outlet and urethra provide such attachment, and are a major factor in the maintenance of urinary control.

### Summary

The selection of twelve patients with urinary stress incontinence forms the basis of this study. Simple vesicourethral suspension as described by Marshall and his co-workers was the procedure used to correct their complaint. An evaluation of the clinical and anatomical findings observed before correction, particularly with the aid of cystography, showed that failure of the pelvic floor, especially of the levator ani, to support the vesical sphincter mechanism

was most frequently associated with loss of urinary control. Cystography postoperatively revealed the striking degree of elevation of the bladder and its outlet effected by the operation. It further demonstrated that the procedure fixes the urethra to the posterior surface of the symphysis without distortion. Although suprapubic vesicourethral suspension is not meant to supplant the standard vaginal operations for the relief of stress incontinence, some of the advantages are enumerated. It is indicated, as a result of this study, that the mechanism of the operation's success lies in the fact that it restores a relatively firm point of attachment to the sphincter mechanism of the vesical neck, a major requirement for the normal function of any sphincter.

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### Discussion

DR. JAMES R. MILLER, Hartford, Conn.—A short time ago I reported at this Society this same operation, devised by Hepburn for the correction of prolapse of the urethra, and I made it plain that we were not speaking of the incomplete and partial prolapse but of the real one, where the urethra turns itself inside-out. The first patient I had was seventy years old and, as Dr. Marchetti has said, the procedure is extremely simple. Following operation this patient voided without difficulty and without a catheter. About six months later I did a LeForte operation.

I would commend this surgical procedure for consideration. The exposure is excellent. I have never done it for stress incontinence but have used it in five patients with prolapse of the urethra.

DR. T. C. PEIGHTAL, New York, N. Y.—Dr. Marchetti has described to us what may well be one of the most important contributions to the operative attack on that often perplexing problem of stress incontinence. Most of us are familiar with his report recently published conjointly with Drs. Marshall and Krantz, giving the technique of this vesicourethral suspension operation, the preliminary test essential to selecting candidates for this procedure, and the end results in thirty-eight cases. The 8 per cent of failures in this first group may well be attributed to the vagaries of developing a new operative procedure.

The additional study of twelve cases in which this operation was carried out personally by the author forms the basis of today's report. These cases comprise varied examples of stress incontinence in middle-aged and elderly patients, in nulliparas and multiparas, in many of whom other operations for relief of this troublesome symptom had failed.

The alteration in the technique of placing the periurethral sutures, namely, in the vaginal wall only, rather than including the urethral wall as described in his original article, is a distinct improvement and in the hands of various operators will help to prevent urethral injury. The necessity of placing supportive sutures in the bladder neck and lower bladder wall to the upper posterior symphysis or lower abdominal wall fascia is properly stressed.

The removal of the indwelling Foley catheter at the end of the operation we hesitate to endorse without trial, since most of these cases have some hematuria for forty-eight hours and it seems to us that retention of the Foley catheter over this period is desirable so that small clots, if present, may be washed out by frequent irrigation. How-

ever, we agree that the catheter should be removed as early as possible since these patients void promptly and, for the most part, have no residual urine. Since this operation results in a very dry field, drainage through the wound of the space of Retzius is seldom necessary or desirable.

By his cystographic studies Dr. Marchetti has shown convincingly both the anatomic bladder defect in stress incontinence and how his operation overcomes this defect. His theorizing on the injury to and the repair of the supports necessary to proper function of the vesical sphincter mechanism is sound.

A preliminary report of the Marshall-Marchetti pin-up operation, by which name this vesicourethral suspension has come to be designated in New York, was given at the New York Obstetrical Society in May, 1948. It came to me personally at a time when I was dissatisfied over the number of essentially poor results we were obtaining on our service with the Kennedy type of fascial plication repair for stress incontinence which we have used for some years, and when the use of urethral supporting fascial strip from the abdominal wall, while for the most part successful in our clinic, were resulting in too many complications, such as overcorrection, failure of strips to hold, and one or two instances of urethral damage. Therefore, the possibilities of the procedure which Dr. Marchetti has described seemed most acceptable: its technical simplicity, its lack of risk, particularly in elderly patients where length of operative time is important, its fresh field of approach through the space of Retzius rather than through the multiple scars of former vaginal operations, and its reported high degree of success with a minimum of complications, convinced us to give it a try.

Accordingly, since last August we have done the operation on five patients in all of whom one or two previous vaginal operations for stress incontinence had been performed with poor results, there in our own clinic. Their ages were 41, 53, 60, 69, and 74 years. One was nulliparous, one para ii, and three para iii. Leakage had been noted from one to ten years. As to results, four have been wholly satisfactory and one (our second attempt at this procedure) was a complete failure due to the breaking away of our suture supports from the coughing of postoperative atelectasis. Since this experience we have placed packing in the vagina as a splinting support for forty-eight hours. However, this is probably an unnecessary precaution in most cases.

Our experience has convinced us that Dr. Marchetti and Dr. Marshall have devised an operation for stress incontinence which is not time consuming, which is easy of execution, which can be combined with both other abdominal and vaginal procedures, which is particularly adaptable and effective in cases where other measures by the vaginal route have failed, and which promises to give results far superior to any fascial strip transplant procedures which have been devised to date.

DR. R. GORDON DOUGLAS, New York, N. Y.—Last week the ninetieth operation according to the technique described by Dr. Marchetti and Dr. Marshall was performed in our Hospital (New York Lying-In). The results have been satisfactory in 87 per cent of the patients, although in many instances the period of follow-up is not long.

I have one suggestion to make in respect to Dr. Marchetti's cystographic studies; viz., that a true lateral cystourethrogram better demonstrates the position of the bladder neck than an anteroposterior plate. In our clinic, we have completed research by means of a true lateral cystourethrogram utilizing a modified Foley catheter filled with 30 per cent sodium iodide for contrast. The bladder neck can thus be marked in relation to the symphysis in the standing and sitting positions and while the patient is at rest or attempting to void. This method has been useful to us particularly in studying the recurrent cases. It has another practical application in that it guides the operator in correcting the anatomical displacement of the bladder neck and urethra.

DR. MARCHETTI (Closing).—I failed to mention that our cystographic findings before operation, in general, are in agreement with those recently published by Muellner.

I appreciate Dr. Douglas's suggestions. We are planning to do a study on urethral visualization by using opaque substances.

# LIGATION OF THE VENA CAVA AND OVARIAN VESSELS\*

## A Follow-Up Study of 59 Cases

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THE dramatic response obtained in a patient with acute suppurative pelvic thrombophlebitis by ligation of the inferior vena cava and ovarian vessels performed Feb. 2, 1942, by one of us (C. G. C.) led to treatment by this procedure of other patients failing to respond to a medical regimen. The results obtained in our earlier cases were reported in May, 1942.<sup>1, 2</sup> Subsequent communications<sup>3, 4</sup> have appeared as the series has increased. To date, fifty-nine consecutive patients with ligation of the vena cava and ovarian vessels have been observed. The youngest patient was 15 years old and the oldest was 65 years old. Six of the operations in the series were performed by members of the Department of Gynecology and Obstetrics of the Louisiana State University School of Medicine, and fifty-three by members of the Departments of Gynecology and Obstetrics of Tulane University School of Medicine. With the exception of two patients, all were supervised preoperatively, at operation, and postoperatively by one or all of us. Most of the patients were under the direction of the senior author. Forty-six patients were treated at Charity Hospital of Louisiana in New Orleans, and thirteen at various private institutions. Repeated follow-up observations of these patients by us and detailed studies of the vascular status of the extremities by Drs. Ray, Burch, Winsor, and their associates in the Department of Medicine, Tulane Medical School, form the basis of this report. Twenty-seven of the patients have been followed from two to seven years and twenty-five less than a year (Table I).

TABLE I. YEARS FOLLOWED IN 52 CASES

YEARS FOLLOWED	NO. CASES
0-1	25
1-2	7
2-3	7
3-4	6
4-5	2
5-6	0
6-7	5

\*Presented at the Seventy-Second Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 16 to 18, 1949.

It is to be emphasized that ligation was performed on patients only if they failed to respond to the medical therapy popularly employed at that time. Patients admitted with pulmonary infarction constituted the sole exception in that they were immediately subjected to ligation. When sulfonamides, penicillin, and streptomycin became available, they were used in accepted dosage. During the past year, these preparations have been given in combination. In a few patients dicumarol, heparin, or a combination of the two, was also given. Thus, operation was performed on those critically ill patients with the most severe inflammatory processes who proved to be resistant to all other therapy.

### Indications

The high mortality rate associated with nonoperative therapy in suppurative pelvic thrombophlebitis prior to 1942, the futility of ligation of the ovarian vessels alone or in combination with one or more of the major pelvic veins, and the good results obtained in our earlier cases in which the normal venous return from the uterus was interrupted, i.e., ligation of the vena cava and ovarian vessels, led in June, 1942, to a formulation of indications for ligation. It was hoped that, with the advent of many chemotherapeutic and antibiotic agents, this suppurative process might be controlled, but this has not been found to be true in all cases. Furthermore, neither the anticoagulants, nor a combination of anticoagulants, chemotherapeutic agents, and antibiotics have produced recovery in all cases.

It is our opinion today as in 1942 that ligation of the vena cava and ovarian veins is indicated in the following cases:

1. Patients with suppurative pelvic thrombophlebitis who fail to improve after four or five days of medical regimen (blood, chemotherapy, antibiotics).
2. Patients with suppurative pelvic thrombophlebitis, receiving nonsurgical treatment, in whom pulmonary infarction develops irrespective of the duration of medical regimen.
3. Patients with suppurative pelvic thrombophlebitis and evidence of infarction on admission. Operation is performed on these patients *immediately*.
4. Patients with large pelvic tumors complicated by phlebothrombosis, thrombophlebitis, or both, involving the iliac vessels.

### Surgical Approach

In cases of suppurative pelvic thrombophlebitis following abortion, delivery, irradiation, or complicating pelvic abscesses the transperitoneal approach is employed, since a successful result in these cases depends upon ligation of the normal venous return from the uterus, and by the transperitoneal approach both ovarian vessels and the vena cava can be inspected and ligated. In patients with suppurative pelvic thrombophlebitis following hysterectomy, the vena cava may be ligated extraperitoneally, as the continuity of the ovarian vessels with the pelvic veins has already been interrupted at the time of hysterectomy. The same approach is indicated in cases of phlebothrombosis involving the common femoral vein or veins (or higher) in both sexes.

### Case Mortality Rate

Of the 59 patients, 52 survived (88 per cent) and 7 died (12 per cent) (Table II). The diagnosis of suppurative pelvic thrombophlebitis was substantiated at operation or autopsy in all the patients who died. All patients who died within one year of operation were considered operative failures, since it is our belief that nothing was accomplished if the patient died of dis-

The fact that penicillin therapy will usually disinfect the postpartum uterus, as suggested in this study, has the possibility of wide practical use. Further investigations on a large scale, however, will be necessary in order to confirm the clinical applications here suggested.

### Summary

1. Uterine cultures were taken from 86 postpartum patients, 54 of whom received varying amounts of penicillin, and 32 of whom received no antibiotic therapy.

2. From 30 of the 32 cultures in the control series from untreated patients, various bacteria were isolated, predominantly anaerobic streptococci and *Bacteroides*.

3. Of the uteri of 54 patients receiving penicillin therapy, 32 were sterile, aerobically and anaerobically, and eight yielded only pleuropneumonia-like organisms.

4. Only fourteen cultures in the penicillin series showed significant bacteria, four of which were penicillin-resistant coliform organisms. All but one of the penicillin-sensitive organisms occurred in cultures taken more than 48 hours after delivery, from patients receiving small amounts of penicillin.

5. The possibility of disinfecting the postpartum uterus by penicillin therapy has obvious clinical applications.

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been our experience. The critically ill patient is the one who most needs it. Most of the deaths in this series were caused not by the operation itself but by *delay* in operating.

TABLE III. DEATHS

PATIENT	ADMITTED	OPERATED UPON	DIED	CAUSE OF DEATH
H. A.	4/15/42	4/18/42	4/18/42	Peritonitis, pulmonary infarct, splenic infarct, postabortal pyometra, thrombus which involved superior vena cava and auricle of heart, postabortal (autopsy)
A. B.	3/15/42	3/20/46	6/28/46	Ruptured mycotic aneurysm, inferior mesenteric artery, acute bacterial endocarditis superimposed on old rheumatic valvulitis, postabortal (autopsy)
E. F.	6/ 8/46	6/21/46	7/14/46	Subacute bacterial endocarditis, postabortal (clinical)
M. T.	1/ 4/45	1/25/45	1/30/45	Septicemia, postabortal (clinical)
G. C.	12/16/47	12/18/47	12/23/47	Septicemia ( <i>Staphylococcus aureus</i> ), postabortal (clinical)
F. S.	9/30/48	10/ 9/48	11/17/48	Possible lupus erythematosus, fibrinous pericarditis, granular vegetations of mitral valve, retained secundines, postabortal (autopsy)
M. A.	8/30/46	9/11/46	9/20/46	Uremia, pyelonephritis, pleural effusion, bronchopneumonia, pulmonary tuberculosis caseous right lobe, perirectal abscess, infarct of spleen (massive hemorrhage from abscess wall) (autopsy)

Three patients died of unrelated conditions, two, three, and two years, respectively, after operation. As can be seen in Table IV, in no way could death be attributed to complications of the procedure. Until the time of death all had normal menstrual function, exhibited no evidence of edema or ulceration of the extremities, and led a normal active life.

TABLE IV. LATE DEATHS

PATIENT	OPERATION	DEATH	CAUSE OF DEATH
O. D.	1942	1944	Arsenical encephalopathy
G. L.	1942	1945	Third degree burns of body
J. D.	1942	1944	Hemorrhage at time of lobectomy

### Condition of Lower Extremities

The channels involved in the passage of blood from the pelvis and lower extremities following ligation of the inferior vena cava have been repeatedly studied. Recently, Robinson,<sup>6</sup> from an excellent review of the literature on this subject as well as from his own experimental work, concluded that the vertebral, azygos, and portal systems of veins are the most important routes of collateral circulation and the superficial veins of the trunk are the least important. Infra-red photographic studies by us substantiate the latter statement (Figs. 2 and 3).

Immediately following ligation of the inferior vena cava, mild edema of the leg and ankle is noted in most cases, but it usually disappears completely within a few weeks or months. Retrograde thrombi occasionally develop but respond readily to lumbar sympathetic block. In nearly all of our patients the right or left lumbar sympathetic chains, or both, were severed at the time of ligation, or lumbar sympathetic blocks were performed postoperatively on the uninterrupted side or sides. We believe that such procedures are valuable adjuncts in relieving

tant metastasis even though the vena cava and ovarian vessels were successfully ligated. It is important to note that the highest case mortality rate occurred in 1946 (Fig. 1), when penicillin became available to us. In an attempt to evaluate accurately its use in suppurative pelvic thrombophlebitis, operation was delayed in two cases longer than our surgical judgment deemed advisable. In fact, four of the seven patients who died were operated on from nine to twenty-one days following admission to the hospital. In our experience, if chemotherapy and antibiotics are to produce results, great improvement will be noted within four to five days following their administration.

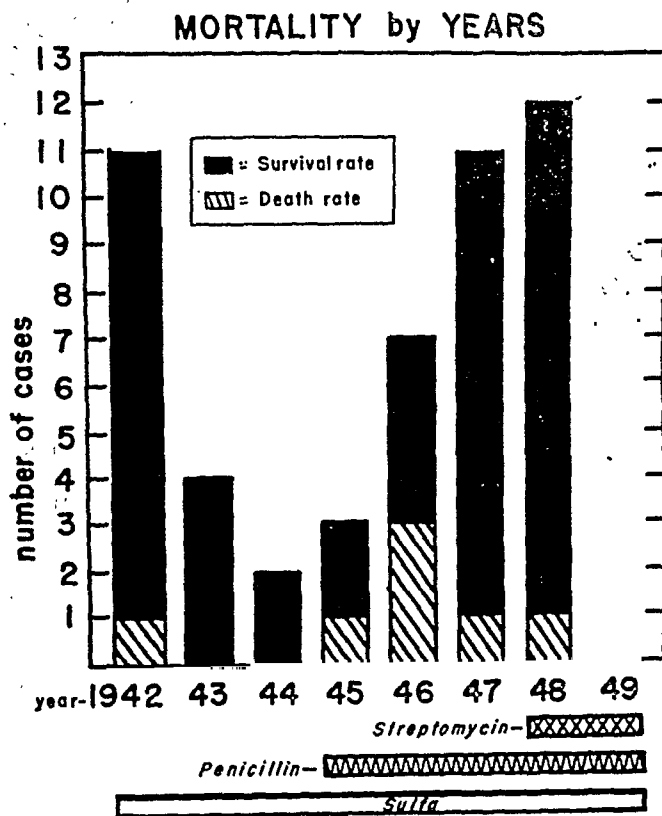


Fig. 1.

TABLE II. CASE MORTALITY RATE (UNCORRECTED)

PATHOLOGIC PROCESS	CASE	LIVED	DIED
I. Suppurative Pelvic Thrombophlebitis.—			
1. Acute			
(a) Puerperal	48	42	6
(b) Posthysterectomy	5	5	0
(c) Postradiation	1	1	0
(d) Perirectal abscess	1	0	1
(e) Posttraumatic	1	1	0
2. Chronic	1	1	0
II. Phlebothrombosis Complicating Uterine Fibroids	2	2	0
Total	59 (100%)	52 (88%)	7 (12%)

In only one case might the procedure itself have been responsible for death, as this patient died immediately following operation (Table III). However, the pathologic condition noted at operation and autopsy makes this questionable. Although ligation of the vena cava upon a critically ill patient has been considered by some<sup>5</sup> to result in a high mortality rate, this has not



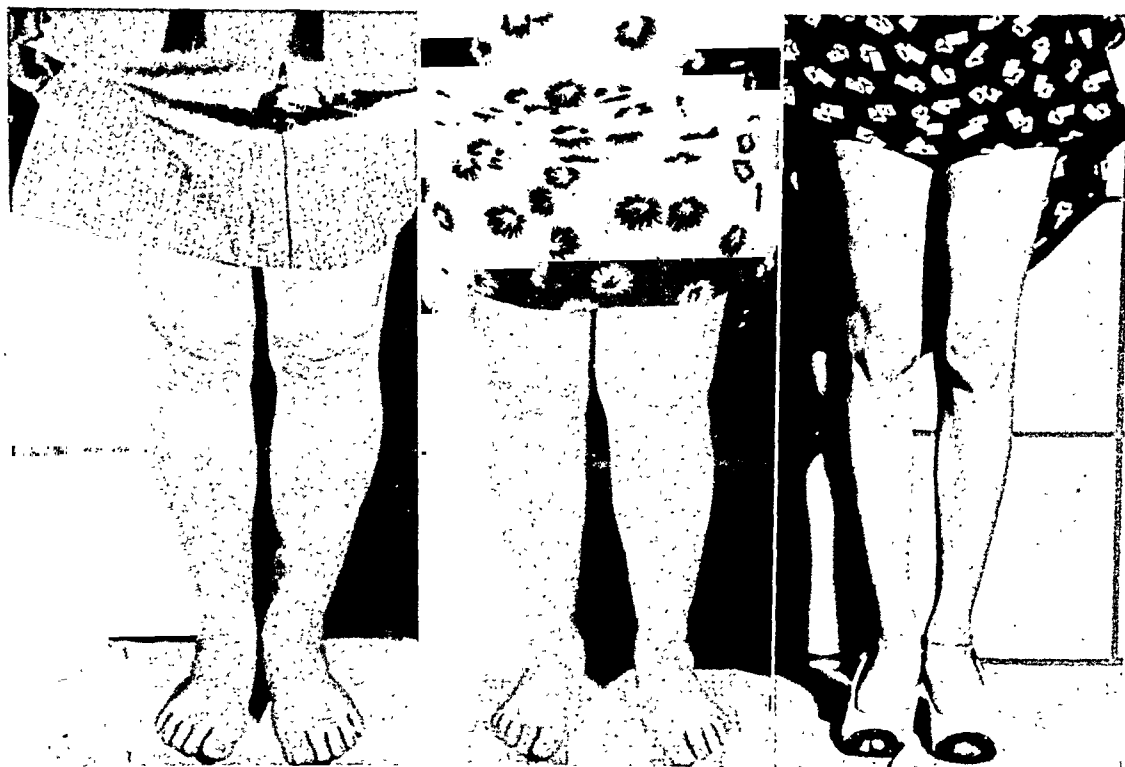


A.

B.

C.

Fig. 3.—Infrared photographic study of veins of extremities. A, Case A. L., varicosities and post-caval ligation (two years). B, Control, no history of vascular disease. C, Case J. D., post-caval ligation, three months.



A.

B.

C.

Fig. 4.—Edema and ulceration. A, Case A. L., varicosities, post-caval ligation (two years), ulceration over both medial malleoli. Only two patients in the series had ulcerations. B, thrombophlebitis of leg of eleven years' duration; sympathectomy, unbridling left femoral vein; post-caval ligation (two years); this was the only patient in the series showing this degree of edema. C, post-caval ligation (two years); this is a typical result.

the arterial spasm occasioned by ligation of a large venous trunk and that the absence of postoperative complications in the legs is in no small part due to these precautionary measures. Pronounced edema of the extremities followed ligation of the vena cava and ovarian vessels in a few patients; this usually occurred in those patients in whom retrograde thrombi developed or in those who had had previous evidence of intravascular clotting in the venous drainage from the lower extremity prior to caval ligation. To date, nine patients still have edema, which is mild in all except one patient, who had recurrent phlebitis and edema of eleven years' duration. On Dec. 9, 1946, lumbar sympathectomy was performed in an attempt to reduce the swelling, and unbridling of the left common femoral vein was done in March, 1947. On May 8, 1947, the inferior vena cava was ligated. Since then, the phlebitis has not recurred and the patient's condition is much better than before ligation, though edema persists and is greater than in any of our other patients (Fig. 4, B).



Fig. 2.—Infrared photographic study of veins of abdominal wall. A, Case M. H., normal term pregnancy. B, Control, no history of vascular disease. C, Case J. D., post-caval ligation, three months.

In two patients ulceration developed over both internal malleoli. In one patient severe varicosities were present for years prior to operation, and discoloration and edema were evident preoperatively about the malleoli. The vena cava and ovarian vessels were ligated July 9, 1947, but the patient failed to wear elastic stockings or ace bandages on returning home. She was again seen in January, 1949, when the ulceration was detected. She was given elastic stockings to wear and the ulcers are healing (Fig. 4, A). However, all this time she has performed all her household duties for a family of seven. The other patients in whom ulceration developed had the severest preoperative thrombophlebitis of the leg and pelvic veins that we have encountered. Following ligation of the vena cava a retrograde thrombus developed on the opposite side but edema in the involved leg subsided rapidly. Two years after ligation ulcerations developed over both medial malleoli. Wearing elastic stockings resulted in complete healing within a few weeks. This patient is the wife of a farmer and has not been incapacitated in the performance of her routine household and farming duties.

In four patients operation was performed during the past three months and edema of the ankles is noted in the evenings after the patients have been up and about all day. Each month brings less edema and it is highly probable that these patients will be entirely free of symptoms within a month or two, as have the others in the series who had mild edema following operation. In two other patients operated on for femoral and suppurative pelvic thrombophlebitis, mild edema of the ankles is noted in the late evening but there is no limitation of activity. All except one patient wear the same type and size of shoe that they wore prior to operation.

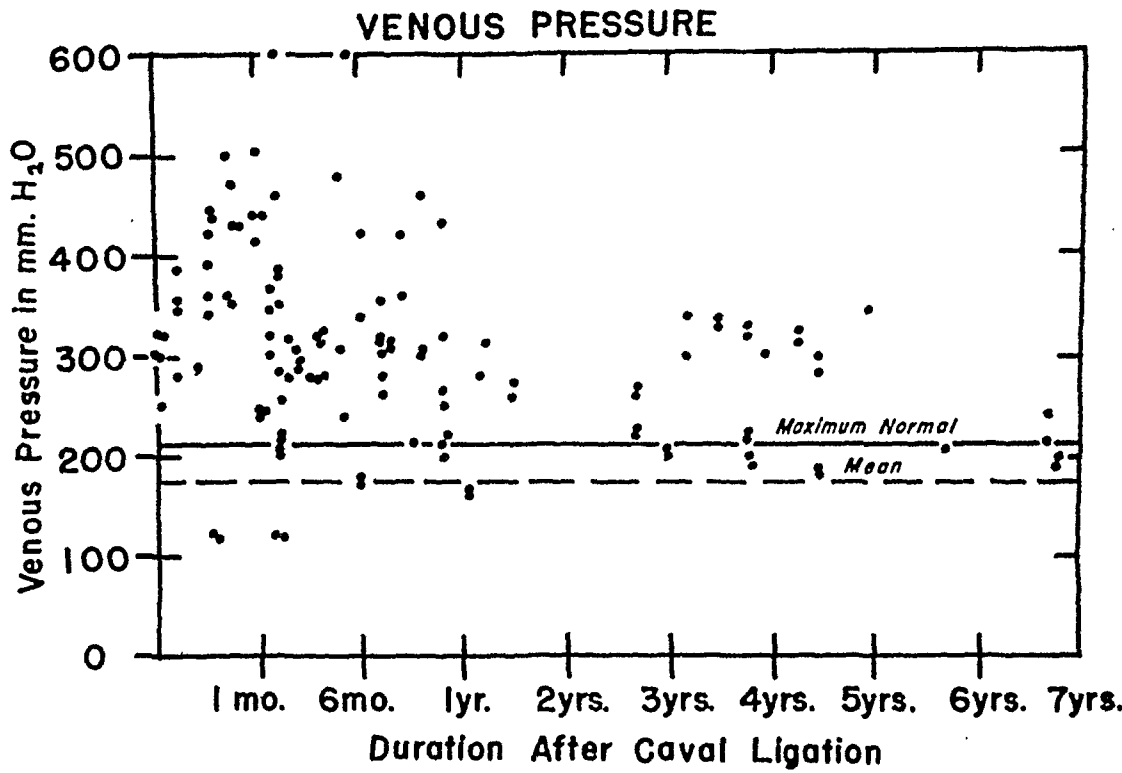


Fig. 6.

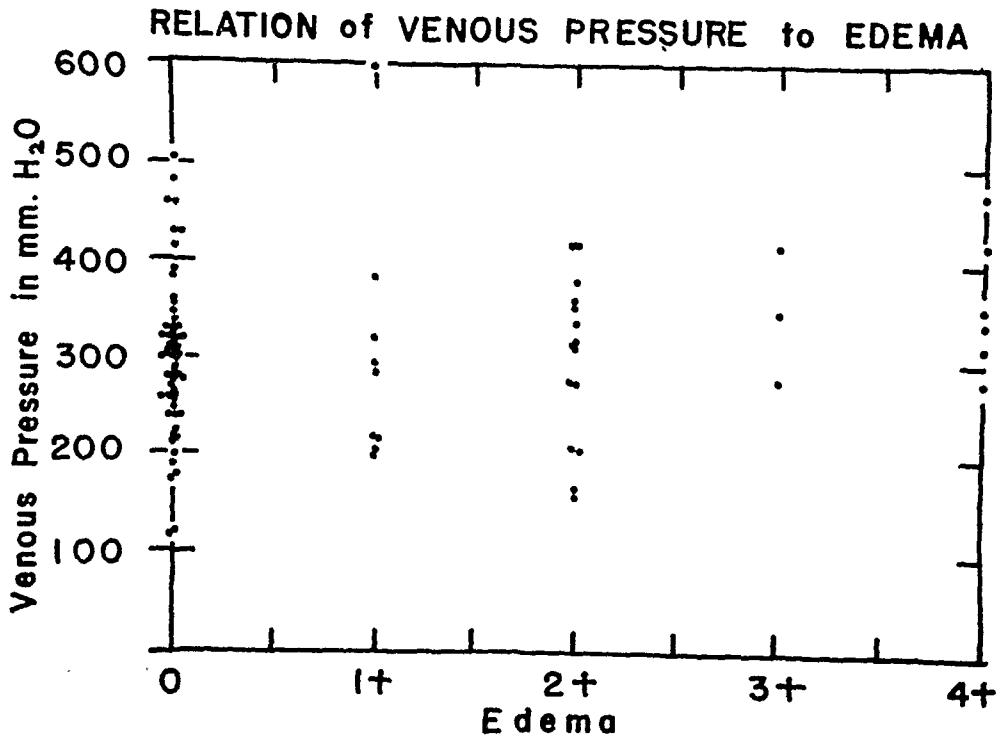


Fig. 7.

### Evaluation of Vascular Status

Certain physiologic observations made in the Tulane Department of Medicine revealed some interesting findings. The venous pressures in the veins of the lower extremities varied from low normal values (120 mm. of water pressure) to exceedingly high values (over 600 mm. water). In the initial determinations few fell within the limits of normal. In the same patients there were differences in the pressures in the two sides (Fig. 5). With time there is a decline in pressures toward normal and in a number of instances to within normal limits (Fig. 6).

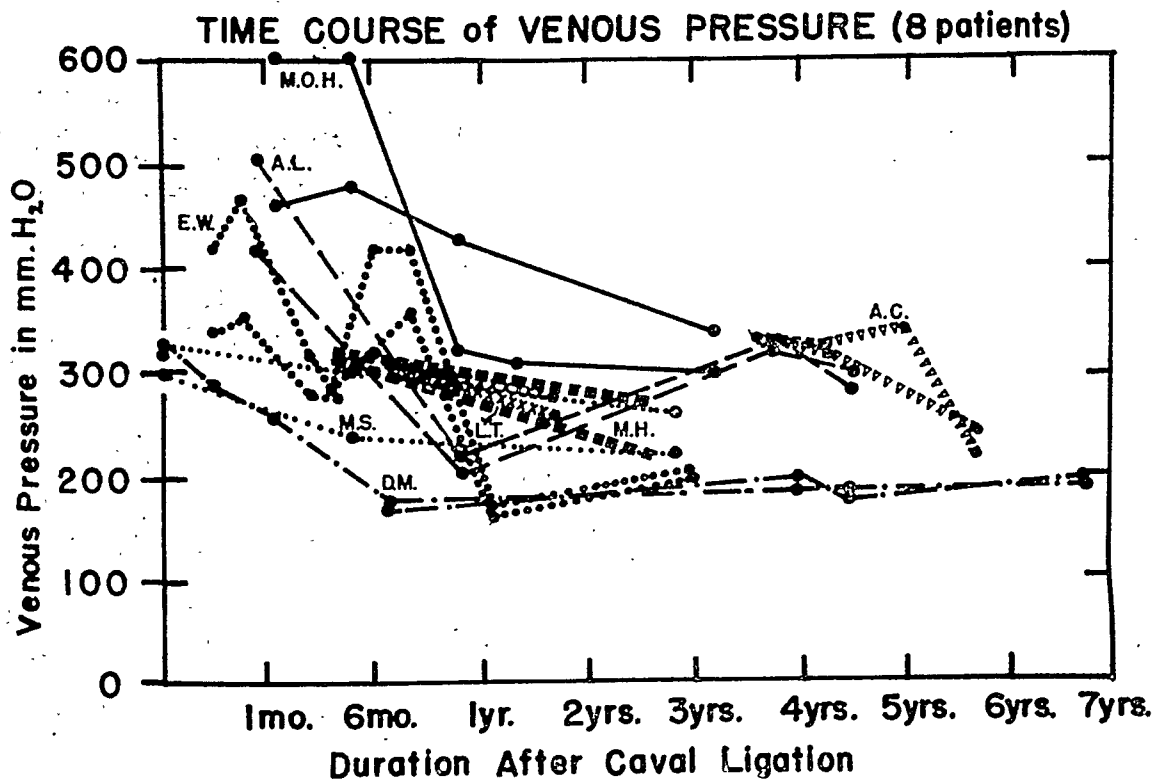


Fig. 5.

As stated previously, edema of the lower extremities is usually present immediately after operation, but it does not always occur. The degree of edema varied from a trace to 4 plus, but in all instances has not persisted beyond the sixth month after operation, and in most of the patients edema completely subsided by the sixth week. The degree of edema was not related to the venous pressures (Fig. 7). In some, edema was pronounced with moderate or relatively low pressures; in others with notably high venous pressures there was no edema. In some the edema which was present initially disappeared without a change in venous pressure. From these observations one can conclude that although venous pressure plays a role in the development of edema, it is not the sole or major factor.

Tissue pressure increases and venous pressure increases were concomitant observations. This would tend to decrease the formation of edema. Plethysmographic studies of the toes revealed pulsations which were somewhat reduced but within the limits of normal. Sympathetic section increased the pulse deflections. Measurements of circulation time from foot to heart, by means of a radioactive isotope, revealed variable durations but all were within normal limits.

These observations, although not clearly defining all the circulatory adjustments, do indicate that there is adequate compensation for vena cava ligation.

the thrombosis extending into the renal vein. There were no deaths and the morbidity was not increased in this group. Since then there has been no activity of the phlebitic process.

TABLE V. HYSTERECTOMY AT TIME OF VENA CAVA LIGATION

PATIENT	OPERATION	PATHOLOGY
M. A.	5/25/46	Acute suppurative pelvic thrombophlebitis; partially retained placenta
A. D.	12/10/48	Chronic suppurative pelvic thrombophlebitis; dyspareunia, severe; badly lacerated cervix with severe endocervicitis
E. W.	2/5/46	Acute suppurative pelvic thrombophlebitis; uterine fibroids
H. W.	12/31/48	Acute suppurative pelvic thrombophlebitis; gangrene of uterus

### Subsequent Surgical Procedures

Twelve patients have undergone some surgical procedure since ligation of the vena cava. The dates of vena cava ligation and subsequent operation together with the indications for further surgical measures and end results are shown in Table VI. The response of the extremities to therapy for thermal injury was well within the normal so that it may be assumed that in these patients, at least, cellular metabolism in the extremities was not altered by vena cava ligation. In the four patients requiring hysterectomy (total abdominal) the circulatory status through the lower abdominal wall and within the pelvis was thoroughly studied by us at the time of operation. In all four there seemed to be no increase in vascularity in the incised abdominal wall. The preperitoneal vessels were not engorged or congested and no deviation from normal status could be determined in the deep epigastric vessels except in one case. The broad ligaments in three of the patients were devoid of varicosities, whereas in one patient considerable dilatation of these vessels was noted. On removal of the uterus, in all cases, no more bleeding from the vaginal cuff or other areas was

TABLE VI. SUBSEQUENT SURGICAL PROCEDURES

PATIENT	V. C. LIGATED	SUBSEQUENT OPERATION	INDICATIONS	RESULTS
H. W.	12/31/48	Skin graft 2/12/49	3° burn left thigh Donor site right thigh	Healed 2/28/49 Asymptomatic
M. B.	10/30/44	Compression bandages 12/19/44	2° burn entire left leg	Healed, asymptomatic
G. A.	4/7/48	Dilatation and curettage 11/9/48	Bleeding retained secundines	Asymptomatic
M. S.	5/25/46	Dilatation and curettage 11/26/46	Polymenorrhea endometrial hyperplasia	Asymptomatic
J. D.	'42	Lobectomy '44	Lung abscess	Died
E. P.	6/18/47	Lobectomy 6/30/47	Residua of infarct Gangrene of lung	Asymptomatic
E. W.	9/1/42	Laparotomy and plastic 3/3/46	Residua of infarct Birth injuries	Asymptomatic
D. P.	1/13/45	Cesarean section 11/4/48	Sterilization	Mild ankle edema in evening
D. S.	8/29/48	Hysterectomy 8/29/48	Previous cesarean section	Asymptomatic
P. H.	4/25/42	Hysterectomy 7/9/48	Severe dyspareunia Chronic endocervicitis	Asymptomatic
O. D.	5/2/42	Hysterectomy 7/30/42	Pelvic pain, bilateral tuboovarian abscess	Asymptomatic
A. L.	4/30/42	Hysterectomy 6/15/47	Large fibroid Lower abdominal pain	Asymptomatic
			Chronic cervicitis Chronic bilateral salpingitis	

## Fertility and Ovulation

No detailed effort has been made to determine the effect on fertility in all patients subjected to ligation of the inferior vena cava and ovarian vessels. From the beginning it was assumed that the inflammatory nature of the disease would render the majority of patients sterile or relatively infertile. However, the occurrence of a few pregnancies subsequent to ligation prompted a brief inquiry into the fertility status of these patients.

Of the 59 patients operated upon, 7 died in the hospital, and 16 had sterilizing operations, leaving 36 in whom pregnancy was anatomically possible. Age (fifth decade or over) eliminated three others, and three patients died within three years of operation, so that there were 30 patients in whom conception was theoretically possible.

These patients have not been questioned regarding the desire for pregnancy, attempts at conception, use of contraceptives, or health of the husband. However, the fact that the majority of operations was necessitated by postabortal sepsis indicates a lack of enthusiasm for childbearing. Nevertheless, six pregnancies have occurred to date among five patients, and of these pregnancies four proceeded to term. All term pregnancies ran a normal prenatal course without complications. Embarrassment of the general circulation, dependent edema, leg cramps, varicosities, or other evidence of inadequacy of the collateral circulation did not occur. One patient required cesarean section because of contraction of the pelvis and previous section, but the other three labors were entirely normal, as was the puerperium in all patients. One woman had a miscarriage at four months, and in another criminal abortion was performed at six weeks.

Of the twenty-five remaining patients who have not had a known conception, nine were operated on less than four months ago. This leaves sixteen patients in whom fertility should be investigated. Without fertility surveys in these patients we can only speculate as to how many were really desirous of pregnancy, how many have been rendered sterile by their disease, and how many have suffered reduced fertility because of the operation.

Basal temperature records were considered to be too intricate for the majority of these patients. Among the surviving thirty patients in the reproductive age, five exhibited ovulation by pregnancy. Fifteen of the remainder had endometrial biopsies performed, ten of whom exhibited progestational endometrium, and five estrogenic. Thus, fifteen of the thirty afforded evidence of ovulation, either by pregnancy or endometrial pattern. Eleven patients were not studied from this standpoint (nine were too recently operated upon), and five patients showed an endometrial pattern inconsistent with ovulation. Among these latter five, two were operated on less than three months ago, and in one patient a corpus luteum was demonstrable at exploratory laparotomy.

These observations would suggest that ligation of the ovarian vessels (arteries and veins) and inferior vena cava does not seriously interfere with ovulatory function in the majority of patients.

## Additional Surgical Procedures at the Time of Ligation

Ligation of the vena cava is a relatively simple procedure which is not accompanied by any great degree of shock. As stated before, in many patients the right or left lumbar sympathetic chain, or both, was sectioned at the time of ligation. In a few, unilateral salpingo-oophorectomy for severe thrombosis and infection involving the ovary was necessary. In one patient bilateral salpingo-oophorectomy was performed, as both ovaries were cystic. In four patients hysterectomy was done at the same time, either as a planned procedure or necessitated by the pathologic condition encountered (Table V). In another patient nephrectomy was necessitated by an ectopic kidney on the right side with

hemorrhoidal masses were observed. In patients with an uninfected cervix or vaginal wall, leucorrhea was not noted. No case of vaginal discharge could be attributed to "pelvic congestion." There was no change in any patient's psyche nor was there any alteration in the desire for, or reaction to, intercourse.

### Menstrual Characteristics

Patients requiring operation to correct abnormal uterine bleeding and the pathologic condition encountered are listed in Table VI. One additional patient in whom the vena cava was ligated March 31, 1948, will require hysterectomy; vaginal examination disclosed a retrodisplaced, fixed uterus, and bilateral chronic salpingo-oophoritis; whether the abnormal bleeding is a result of the ligation or the pathologic condition described is a matter of conjecture. One patient has not menstruated since ligation of the vena cava, though none of her genital organs were removed at that time; extensive pyometritis associated with the suppurative process in the pelvic veins is believed to have destroyed the endometrium, resulting in amenorrhea. In all other patients the menstrual pattern is the same as prior to ligation of the vena cava.

### Conclusions

1. Ligation of the inferior vena cava and ovarian vessels is indicated in patients with suppurative pelvic thrombophlebitis failing to respond to medical therapy, regardless of the severity of the illness.

2. Ligation of the vena cava in critically ill patients is associated with a low case mortality rate. The deaths in the present series occurred as a result of the pathologic condition for which operation was undertaken and not as a result of the operation *per se*.

3. The indications for operation in the patients requiring subsequent surgical procedures were not a result of ligation of the vena cava and ovarian vessels.

4. In our series there was adequate compensation for the circulation in the extremities following ligation. No patient was incapacitated.

5. Menstrual or sexual function was not altered by ligation in the majority of patients in our series.

6. Ligation of the vena cava and ovarian vessels (arteries and veins) appears to have little or no effect on ovarian function in women but further studies will have to be conducted to establish this observation definitely. The procedure does not preclude a normal pregnancy or postpartum course.

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### Discussion

DR. RALPH A. REIS, Chicago, Ill.—Three years ago before this Society, Dr. Collins proved that patients would survive preoperative prophylactic ligations of the inferior vena cava and of both ovarian veins. Today he proved that such survival is usually followed by

encountered than at average routine abdominal hysterectomy. The visible retroperitoneal vessels did not seem to be engorged, congested, or varicosed. Palpation of the common iliac veins revealed them to be completely thrombosed and fibrotic in three of the four patients. In one, such was not the case and injection of Diodrast into the left common iliac vein and venography at the time of hysterectomy confirmed the experimental studies previously alluded to in that the major portion of the injected material was found in the lumbar and vertebral areas (Fig. 8). In the patient who had a vaginal plastic operation, suspension of the uterus, and tubal sterilization, and in the one requiring cesarean section, communications from their physicians informed us that there seemed to be no disturbed vascularity at the time of operation. Two patients required lobectomy for residual of the original infarctions which had necessitated ligation of the vena cava. One died at the time of lobectomy as a result of hemorrhage from the operative field; the other is well today. In two other patients in our series pulmonary abscesses developed as a result of the pre-caval ligation infarction but in both of these patients the abscesses healed spontaneously within two or three months, respectively. We are still undecided as to the efficiency of chemotherapy or antibiotics, or both, in the prevention of abscess in pulmonary infarction. In our first twenty-two cases chemotherapy or antibiotics, or both, were discontinued at the time of ligation in an attempt to prove that ligation alone was responsible for controlling the phlebitis. Pulmonary abscess developed in two of these twenty-two patients. In the remaining thirty-nine patients, chemotherapy and antibiotics were continued until the patient became afebrile in an attempt to forestall added pulmonary complications but pulmonary abscess developed in two of them.

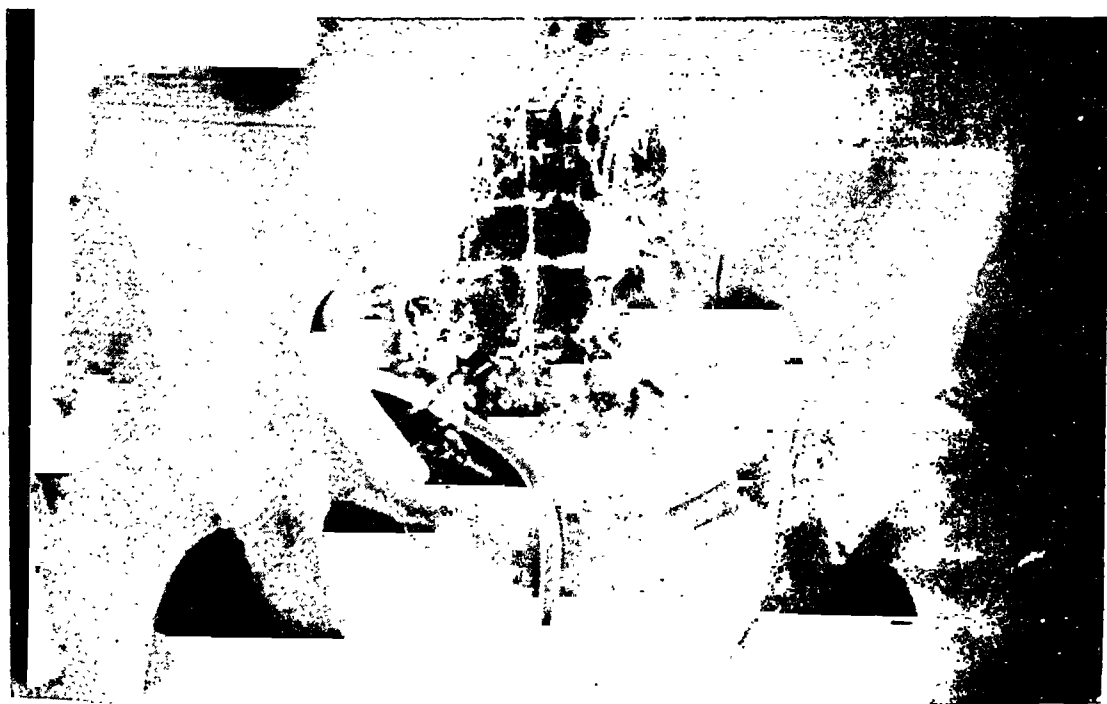


Fig. 8.—Phlebogram of return circulation following ligation of inferior vena cava and ovarian veins taken at time of hysterectomy. Diodrast injected into left common iliac vein. Opaque hook-shaped object is catheter in bladder and urethra.

#### Condition of Vulva, Vagina, and Rectum

In none of the patients did varicosities or discoloration of the vulva, vaginal walls, or cervix occur. The only pathologic alterations noted in these structures at follow-up examination were those resulting from childbirth or infection. No



## EFFECT OF BIRTH ON MENTALITY

MARGARET BATTLE, M.D., ROCKY MOUNT, N. C.

THE purpose of this paper is to show the effect of pregnancy and labor on the intelligence quotient and personality of the infant.

### Method

The 453 cases studied are the children attending the Rocky Mount High School, provided they were born in the city. Also included are the last two years' graduates and the children who withdrew from the high school in the past few years. The earliest birth was in 1926 and the latest in 1933.

All of the fifteen doctors who delivered these patients were general practitioners, but one had two years' residency at the New York Lying-In Hospital. The cesarean sections were done by two surgeons, both Fellows of the American College of Surgeons, and one a member of the American Board of Surgery. One delivery was attended by a midwife.

One hundred forty births were in hospitals; the remaining 313 were home deliveries. No records could be found in the doctors' offices of these 313, other than the names of the mothers and the dates of the deliveries. Six of the doctors were dead, one had moved away, and the remaining eight had moved their offices, or stopped doing obstetrics, and the records were lost. Questionnaires were therefore sent to the mothers.

The accuracy of the answers was better than had been expected. Sixty-nine of the hospital-delivered mothers returned questionnaires showing 89.1 per cent accuracy in reporting spontaneous deliveries, and 92.3 per cent in reporting forceps. The greatest inaccuracy was in reporting breech deliveries. Of 41 reported breeches, only 13 were finally considered so after telephone conversations with the mothers or second questionnaires where no telephone was available. Three of the 13 were not reached but were left in the group listed as breech. This left 2.87 per cent breech deliveries, comparable with the usually reported 3 per cent. The mothers' listing of parity was not questioned. The estimates of weight gain and hours of labor are highly questionable, but no method of checking this could be found, since these were not mentioned on the hospital records. The weights of babies are probably fairly accurate as the home-delivered babies were weighed by the attending doctors. The mothers' ages were taken from hospital records or birth certificates.

The IQ rating was the highest recorded of the 1 to 4 listed on the high school records; this was considered more truly representative of the child's ability. The mental tests were mostly Pintner Cunningham, Pintner Intermediate, and National Intelligence Test. A few were the California Mental Maturity Test and the Stanford-Binet in addition to the above. The personality rating is an average of individual ratings in cooperation, courtesy, dependability, industriousness, initiative, leadership, maturity, self-control, and personal appearance. A personality rating of 1 is superior, 2 above average, 3 average, 4 below average, and 5 low.

good health and physical comfort. We believe that he failed to prove the need for such a procedure either as a prophylactic measure or as a therapeutic procedure for the cure of septic pelvic thrombophlebitis.

His original report quoted statistics from the literature in which postoperative pulmonary embolism occurred in 3 to 4 per cent following pelvic surgery. Of the deaths studied at Charity Hospital fifty, or 9 per cent, showed intravenous clotting and eight of these fifty had pulmonary embolism. Eleven patients with septic pelvic thrombophlebitis of obstetric origin were subjected to ligation of the inferior vena cava and of the ovarian veins. Two of these eleven patients died subsequently. In addition three patients with postoperative septic pelvic thrombophlebitis were treated in the same manner and all recovered. The present report concerns fifty-nine consecutive ligations with seven deaths. Because of these results, Dr. Collins recommends prophylactic ligations for large tumors with evidence of venous obstruction and pressure symptoms and further recommends similar ligations for septic pelvic thrombophlebitis since in his experience 85 per cent of such patients developed lung infarctions.

It is difficult to reconcile these figures and these recommendations with our own experience at Michael Reese Hospital. During the past ten years we have had 21,830 deliveries with seventeen deaths, or one death in each 1,284 deliveries. During this time pulmonary embolism was diagnosed only four times and, of these, one terminated fatally. This followed cesarean section, wound disruption, and sepsis. It would be most difficult to justify prophylactic vein ligations in any one of these 21,830 women.

Zimmerman, Miller, and Marshall have just reported the total Michael Reese Hospital experience with pulmonary embolism during the last seventeen years. Based on nearly 6,000 post-mortem examinations during this period in which 152,371 major surgical operations were performed, the incidence of fatal postoperative pulmonary embolism was 0.05 per cent, or one in every 2,000 major operations. Ten of these fatalities followed gynecological surgery and here again the incidence was approximately one in every 2,000 major gynecological operations. Five of these ten patients were suffering from malignancies of pelvic origin. It would likewise be most difficult to justify prophylactic vein ligations in this huge operative group.

The authors have stated that "Charity Hospital is a dumping ground" and that septic pelvic thrombophlebitis is relatively frequent and severe. We do not share in this experience. Michael Reese is a large general hospital with both private and service patients and our own experience with septic pelvic thrombophlebitis—both puerperal and postoperative is more limited than is our experience with pulmonary embolism.

It is difficult to accept the authors' dictum of venous ligations for this condition. Long experience of the European gynecologists led all but a small group in France to abandon venous ligations long before the last war. This was done because of the difficulties in diagnosis and because of the failure to improve their statistics. In Dr. Collins' paper, the mortality after ligations was given as 12 per cent. Our own experience gives a lower mortality without ligations, and one wonders how many patients were operated upon for mortality without ligations, and one wonders how many patients were operated upon for the purpose of vein ligation who did not prove to have septic pelvic thrombophlebitis. It would seem, in this era of chemotherapy, antibiotics, and anticoagulants, that the addition of further surgical trauma to patients already critically ill from septic pelvic thrombophlebitis is unwarranted and may prove disastrous. One wonders why anticoagulants were used in "only a few cases."

In recent years we have been deluged with most enthusiastic reports of the merits of venous ligations for postoperative phlebothrombosis and thrombophlebitis; for example, one report of bilateral femoral vein ligations in 458 patients over 65 years of age followed by only one death from pulmonary embolism. In a comparable group of 458 without ligations, the thromboembolic syndrome occurred 58 times (1 in 8) and resulted in 26 fatal pulmonary emboli (1 in 17). Zimmerman and his group have estimated from their studies, that Michael Reese Hospital would have to have not 458 but 52,000 consecutive major operations to furnish the same number of deaths from pulmonary embolism. This means 1,140 times as many operations.

We venture the prediction that the ligation of major veins as prophylaxis or as therapy for puerperal and postoperative phlebothrombosis and thrombophlebitis will decrease in the coming years and that the enthusiasm for this procedure will steadily and rapidly wane.

DR. JOE V. MEIGS, Boston, Mass.—We see very few cases such as Dr. Collins has reported, but ligation of the vena cava is, and can be, done, but should not be, unless it is essential. Members of our hospital staff have recommended the ligation of veins as a prophylactic step to prevent embolism and in patients with vein involvement. Actually, we have done very few lately on our Gynecologic Service. Our patients now receive dicumarol in very moderate doses. However, if I had phlebothrombosis or an embolism which was not fatal I would choose to have my veins ligated. I would not care to take a chance on dicumarol or heparin if I knew I had a vein that was involved.

I think you have to ligate some veins and I agree that in some few cases we should ligate them prophylactically.

The more we watch and observe vein troubles the more we will be able to evaluate the procedure advocated by Dr. Collins. We will do fewer but we will not discard the procedure, I am sure.

DR. T. K. BROWN, St. Louis, Mo.—Ligation was done a few times in St. Louis in 1924 to 1928 without very satisfactory results. At that time the mortality throughout the country was about 50 per cent after such operations. This has been greatly improved where the operation is done more routinely, and I think one of the outstanding reasons for this improvement is that ligation has been done at an earlier time than it was in the past. Formerly it was a desperate procedure done as a last resort in most cases.

In 1924 Dr. Schwarz and Dr. Dieckmann showed the importance of anaerobic bacteria as the cause of thrombophlebitis in their work on puerperal infection. Shortly thereafter we were able to reduce the need for radical treatment in these cases if the uterus is treated early when it is the focus of infection, and if the site of infection is removed these subsequent complications have not occurred. Later the value of instillations of acriflavine and glycerine was shown, and since 1930 we have not had a death from thrombophlebitis on our service in St. Louis Maternity Hospital. Also since 1930 and with instillations of acriflavine and glycerine we have had no deaths from puerperal infection in some 37,000 deliveries. We have obtained similar results on our service at the St. Louis City Hospital No. 1, which is for white patients, and at Homer G. Phillips Hospital, where we see only Negro patients. These are both large services and we have not seen cases of severe thrombophlebitis or lung abscess in recent years. I would like to stress that the administration of sulfonamides and penicillin has played no role in the figures I have quoted.

DR. COLLINS (Closing).—We still see suppurative pelvic thrombophlebitis. I would like to emphasize that we saw many more than the forty-eight patients operated upon, but the latter were the ones that failed to respond to sulfonamides, penicillin, or streptomycin, and in a few cases dicumarol and heparin. In the pelvis where the disease process is not simply a clot but a suppurative process within a clot, that patient dies not of pulmonary embolism but of repeated small infarcts to the lung, liver, kidneys, and brain. If they do not respond to conservative treatment within five days ligation is necessary.

As regards phlebothrombosis or thrombophlebitis of the veins of the extremities, we do not use ligation or anticoagulants prophylactically to prevent embolism. We wait until clinical signs develop. There is no argument about anticoagulants as against ligation. The object is to prevent embolism and whether we use one or the other or both is immaterial. We believe if operation is to be of value in suppurative pelvic thrombophlebitis, five days is the limit of medical regimen.

Time does not permit a discussion of the diagnosis or pathology encountered.

## INDUCED MENSTRUATION FOR METRORRHAGIA AND AMENORRHEA\*

LAMAN A. GRAY, M.D., LOUISVILLE, KY.

*(From the Department of Obstetrics and Gynecology, University of Louisville School of Medicine)*

THE treatments of metrorrhagia have been numerous and confusing. Probably the most common treatment is curettage of the uterus. This operation, removing the lining from the uterus, when done with care, may be followed in 50 to 60 per cent of the cases with excellent results. Particularly is this true if the irregularity in menstruation had been a minor one and of relatively short duration. The mechanism by which the ovary reverts to a normal cycle following curettage is not clear. The mechanical removal of the endometrium may interrupt some metabolic process of the hormones involving the retained endometrium or a nervous stimulation by a reflex method may cause the ovary to revert to normal or possibly the passage of time and improvement in general health following the temporary cessation of bleeding may have some indirect bearing on the return of the ovary to normal function.

Metrorrhagia can be readily controlled, according to Allbright,<sup>1</sup> by the administration of 5 mg. of progesterone daily for five or six days which will be followed three days later by a menstrual flow which leaves the uterus clean as though it had been curetted. This method of treatment he calls the medical curettage. It is also known somewhat in the literature as the Allbright curettage. In a single paper on this subject, in 1938, Allbright stated that this procedure prevented endometrial hyperplasia until such time as underlying disturbances in the ovarian cycle were corrected. He felt that the treatment did not correct, but merely took care of one of the complications of the disease. He thought progesterone helped in restoring the normal cycle. No cases were reported by Allbright. He stated that the method was first suggested by J. S. L. Brown. An abstract of a paper by Browne,<sup>2</sup> in 1938, in which he used 5 mg. of progesterone in four injections given every other day for the treatment of metropathia hemorrhagica, stated that a therapeutic curettage should first be performed. Otherwise there was a tendency for profuse bleeding following the first course of progesterone. He treated seven cases; two for twenty-eight and nineteen periods, the remainder for shorter intervals. Bleeding, normal in amount and duration, followed each course of injections in one to four days. These doses were inadequate to produce complete progestational change. In fact, little histological change was seen in the endometrium. Amenorrhea, associated with endometrial hyperplasia, was followed by normal periods of bleeding after progesterone thus given.

In three papers by Zondek and co-workers<sup>3, 4, 5</sup> (1938, 1940, 1942) dealing largely with the effects of progesterone on amenorrhea, further observations are important. He found that the administration of progesterone, 10 mg. daily for five days in the postmenstrual phase of the normal cycle, was followed in 60

\*Presented, by invitation, at the Seventy-Second Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 16 to 18, 1949.

hours by a period of apparently normal menstrual bleeding (intracyclic hemorrhage). If the progesterone was given while the patient had her own corpus luteum, bleeding either did not occur or occurred from a progestational endometrium. He felt there must necessarily be an interval between exogenous progesterone administration and endogenous hormone production. In secondary amenorrhea progesterone given 10 mg. daily for five days (in one case, 20 mg. for five days) was followed by an apparently normal menstrual flow. In primary amenorrhea no such bleeding occurred. He concluded that estrogen, though subnormal in amount, must be present for bleeding to occur after progesterone. Imperfectly proliferated endometrium responded to progesterone. Progesterone in doses of 50 to 150 mg. did not interrupt pregnancy. He stated that bleeding after 50 mg. of progesterone took place from a proliferative endometrium. The 50 mg. may be distributed over two days instead of five days. If given in one injection no result was obtained. Zondek felt that progesterone as a therapeutic agent was particularly valuable because it had no injurious effect on the anterior lobe of the pituitary gland and because any possible carcinogenic influence was eliminated. He thought that the progesterone dose (50 mg. minimum) may be reduced if the estrogen level in the body was increased.

In 1942 Allen and Heckel<sup>6</sup> reported the effect of progesterone in adolescent girls and young women with functional uterine bleeding. In twenty-four patients the administration of approximately 30 mg. of progesterone was followed by cessation of bleeding within ten days of the last injection. In one-third, normal cycles occurred for four months or more after therapy, whereas in another third there was a recurrence in less than four months. In the final third amenorrhea followed immediately or after two or three cycles. Treatment was given in courses intermittently. They felt that each course of injections acted similarly to a curettage of the uterus. They postulated that the progesterone might inhibit the estrogen to release the pituitary to more normal function, or that the sudden removal of inhibition from the temporary progesterone might be followed by greater gonadotropic function from the pituitary gland.

Jones and Te Linde<sup>7</sup> (1942) studied the subject of endometrial hyperplasia carefully. First they studied the effect of curettage alone in 111 cases. Approximately half of the group over 35 years was relieved by curettage alone. Of those under 35 years, 40 per cent were relieved by curettage alone. Twenty-eight were treated with progesterone after recurrence, and only two required hysterectomy. They found that progesterone would not control the immediate hemorrhage, and that its greatest use was for preventive purposes. Generally progesterone should be given cyclically for four months. They gave 5 mg. daily for ten days the first month, then for eight days, six days, and four days. Follow-up was by history and not by endometrial biopsy.

Rakoff<sup>8</sup> (1946) reported a series of 51 amenorrheic patients treated with progesterone, 20 mg. intramuscularly, daily for two and three days. Of 44 patients with secondary amenorrhea, 66 per cent responded to progesterone alone. Many of these had subsequent spontaneous bleedings and five became pregnant. The remaining 34 per cent had induced bleeding with progesterone after estrogen priming.

In the Endocrine Clinic of the University of Louisville in the last three years, an attempt was made to study this subject and to determine the value of progesterone in the treatment of functional uterine bleeding and amenorrhea. Various dosages and methods of giving progesterone were studied. The principle of this treatment consists first of the usual cessation of bleeding following continuous absorption of progesterone over three or four days. This is followed

by a period of withdrawal bleeding lasting three to seven days, after which complete cessation of bleeding occurs for a period of several weeks. It is important to understand that withdrawal bleeding follows the cessation of therapy, otherwise the patient and physician are under the impression that the treatment is of no value and has really made the condition worse in many instances. Once the prolonged bleeding has been stopped, repeated administrations of progesterone are given every twenty-eight days, each in turn being followed by withdrawal bleeding which one may predict with reasonable accuracy according to the dose and type of product used.

### Puberty Metrorrhagia

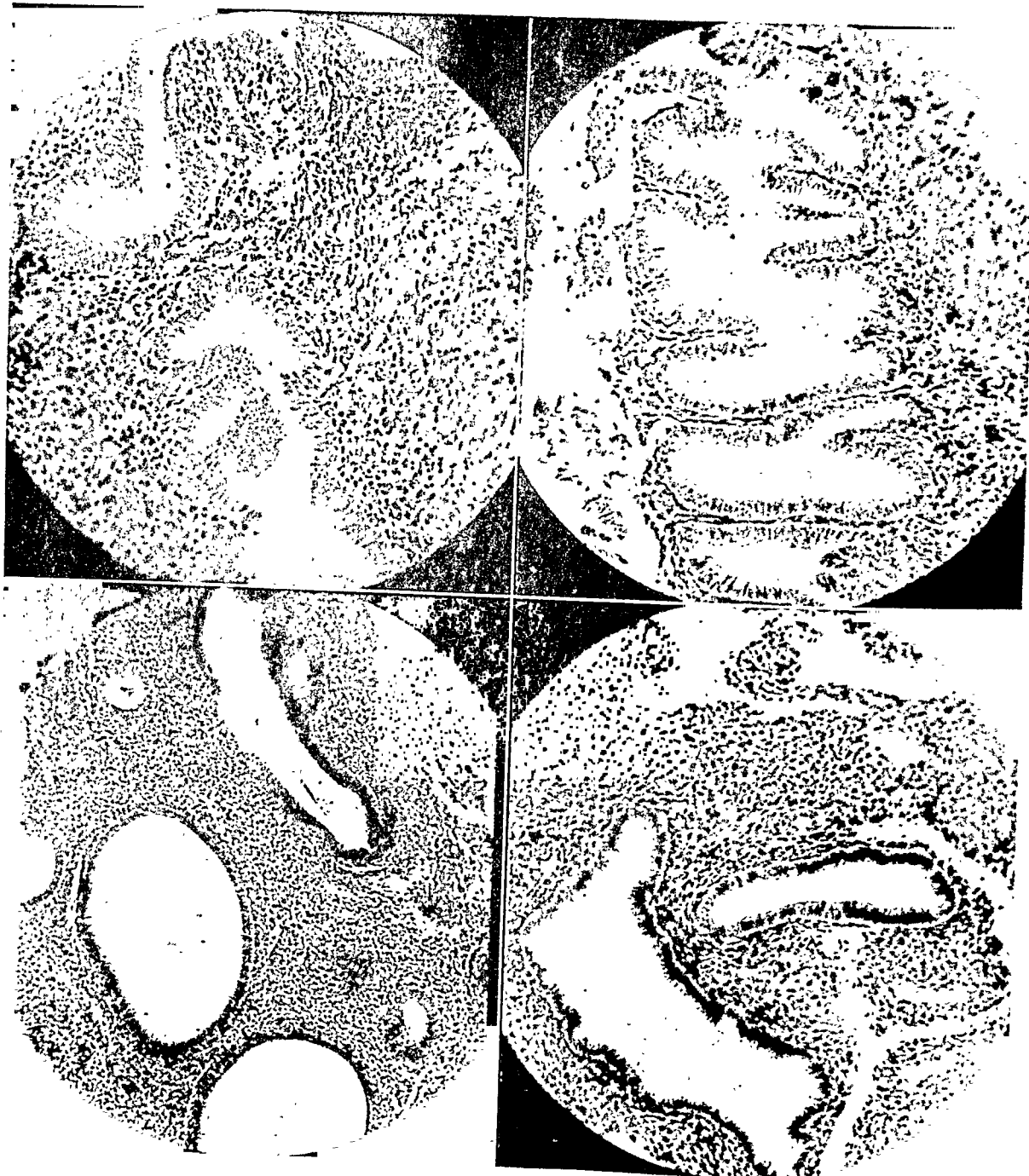
There were eight cases with puberty metrorrhagia. Two were 12 years of age, three were 15, one was 16, one was 17 and one was 19 years old. The older patients had had continuous or almost continuous bleeding since menarche. Three were curetted originally. In four, the first withdrawal bleeding with treatment was not excessive, while in one the first withdrawal bleeding was excessive, requiring transfusions.

These eight patients were treated with courses of progesterone for a total of fifty-three cycles. The largest number of courses (twenty-three) was with progesterone 10 mg. in oil intramuscularly daily for five days. Continuous withdrawal bleeding occurred for five to seven days, or if the patient was not bleeding at the time, simple withdrawal bleeding followed an average of three days later. Similar withdrawal bleeding followed progesterone in doses of 12.5 mg. or 25 mg. in oil daily for five days, also after 25 mg. in oil for three days. Progesterone, 20 mg. aqueous suspension for one dose on three occasions, or three daily injections, induced withdrawal bleeding. Thirteen bleeding episodes followed progesterone, 50 mg. in beeswax-peanut oil, although in three the onset was delayed for fourteen and fifteen days. A single injection of 125 mg. in oil was followed by withdrawal bleeding in two of three cases. In one, apparently the absorption and excretion were too rapid. In one, 125 mg. in oil for two days gave the usual normal withdrawal flow. Four courses of sublingual progesterone were tried, failing with 25, 30, and 50 mg. daily for five days, but giving the usual withdrawal bleeding after 100 mg. for five days.

In three patients biopsies taken before treatment showed endometrial hyperplasia. Sixteen series of biopsies were taken after administration of progesterone. In two, late interval (or early progestational) endometrium was found four days after 125 mg. in oil. One of these biopsied on the sixth day, while bleeding, showed fragmented menstrual-type endometrium, representing a very rapid change to the disintegrated endometrium as found during normal menstruation. The other case had no withdrawal bleeding, possibly because of too rapid absorption and excretion of the single dose in oil; the biopsy on the seventh day showed interval nonsecretory endometrium, reverting from early secretory to nonsecretory intact endometrium in three days. After progesterone, 125 mg. in oil for two days, fragmented menstrual endometrium with some Swiss cheese glands with basal globules were found. After progesterone, aqueous suspension 20 mg. for one day, menstrual fragmenting endometrium was found in two and questionable secretion in a third. When the same dose was given for three days a full premenstrual endometrium occurred seven days later. After 10 mg. in oil intramuscularly daily for five days, premenstrual endometrium was found in one, nonsecretory in one, and insufficient tissue after bleeding in a third. After 12.5 mg. daily for five days, a late interval endometrium (early progestational) mixed with Swiss cheese hyperplasia was followed by fragmented menstruating endometrium during bleeding. Fifty mg. of progesterone in beeswax-

1.

2.



3.

4.

Fig. 1.—Patient H. Y., aged 17 years, Metrorrhagia. Before treatment No. 46-1585. Non-secretory endometrium with hyperplastic glands; continuous bleeding.

Fig. 2.—Patient H. Y., eight days after biopsy (Fig. 1) and three days after progesterone, 10 mg. intramuscularly daily for five days. No. 46-1621. Premenstrual endometrium. Bleeding ceased after third injection and withdrawal bleeding began after this biopsy.

Fig. 3.—Patient H. Y., no recent treatment. No. 47-1347. Endometrial hyperplasia.

Fig. 4.—Patient H. Y., progesterone 125 mg. intramuscularly daily for two days. Second day later, No. 47-1410. Endometrial hyperplasia with some basal globules indicating partial early secretion.

peanut oil was followed by nonsecretory endometrium in one, and insufficient tissue during bleeding in the second. After 100 mg. sublingually for five days, insufficient tissue could be obtained during withdrawal bleeding. After 30 and 25 mg. combined with Urestrin, sublingually for five days, the endometrium remained nonsecretory and no bleeding occurred.

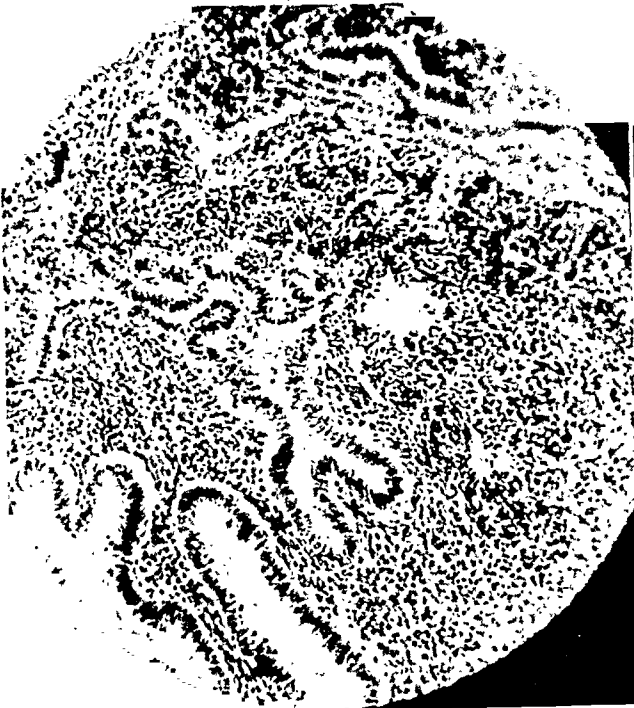


Fig. 5.



Fig. 6.

Fig. 5.—Patient H. Y., fourth day after progesterone. No. 47-1412. Menstruating endometrium with fragmentation and hyperplasia background.

Fig. 6.—Patient H. Y., progesterone 12.5 mg. intramuscularly for five days. Biopsy day of last injection, No. 48-85. Late interval (early secretory) with some Swiss cheese nonsecretory glands.

Secretory endometrium was found after progesterone on eight occasions, and menstruating fragmenting endometrium in five biopsies. Insufficient tissue was obtained three times during bleeding, possibly meaning most of the endometrium had been shed. Nonsecretory tissue was found twice after intramuscular progesterone and after sublingual progesterone when the dose was 50 mg. or less daily for five days. In two above instances secretory changes occurred on a background of Swiss cheese type hyperplasia.

Follicle-stimulating hormone studies were made in three cases. In one patient the titer was high (+53 mouse units per liter), normal (+6.6) and too low (−6.6) in the three samples tested. In the second it was low twice (−6.6), normal twice (+6.6, −53; +6.6). In the third it was low (−6.6). With endometrial hyperplasia and supposed hyperestrinism, one might have expected consistently high values.

Pregnandiol studies showed rapid excretion after 125 mg. intramuscularly, after one day 16 mg., after two days 5.6 mg., and after eight days 1.1 mg. When progesterone, 50 mg., was given in beeswax-peanut oil, the level rose slowly, 2.2 mg., 3 mg., 8 mg., 13 mg., 25 mg., 8 mg., 16 mg., and 0.4 mg. being found on successive days. Progesterone, 100 mg. sublingually for five days, resulted in an excretion of 16.5 mg. after one day of therapy, 10.3 mg. after two days, 16.5 mg. after three days. Two days after cessation there were 4.5 mg., three



days 4.5 mg., and six days 2.8 mg. A marked rise in pregnandiol excretion occurred during sublingual therapy but this rapidly subsided after cessation of therapy. Apparently one injection in oil gives a rapid rise and fall in two days, whereas the beeswax-peanut oil preparation gives sustained excretion levels.

In these eight cases the bleeding was controlled readily with progesterone. Three to four series of treatments in four patients were followed by practical cure (two received thyroid). In a fifth, recurrence followed after six months. The sixth developed amenorrhea. In the last two (aged 17 and 19 years) recurrence of endometrial hyperplasia and metrorrhagia has followed extensive progesterone (and thyroid) therapy. They have had a total of nine and eleven treated cycles.

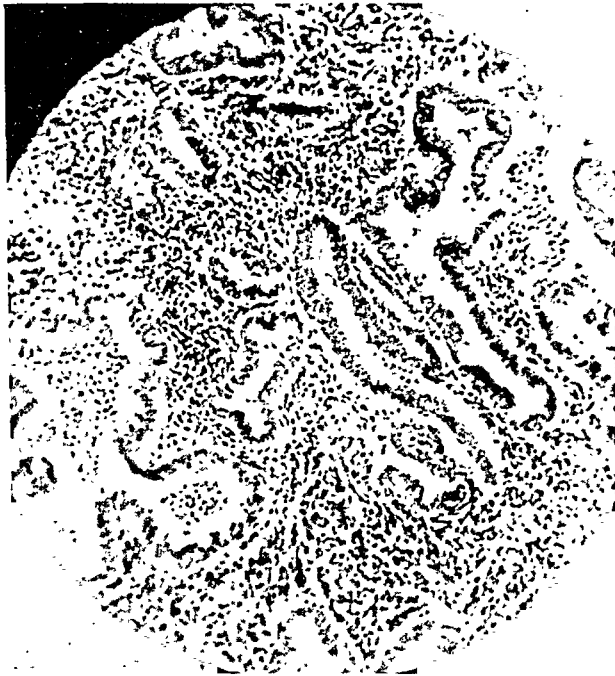


Fig. 7.—Patient H. Y., third day later (after Fig. 6). No. 48-104. Menstruating endometrium with fragmentation and secretion.

Progesterone therapy has given excellent control of bleeding in puberty metrorrhagia. In two of the older patients, permanent cure has by no means been effected. Further controlled bleeding seems indicated in these in order to avert hysterectomy. Possibly spontaneous reversion to ovulatory cycles will occur.

### Metrorrhagia After Puberty

There were thirty cases with metrorrhagia. This group includes those with prolonged bleeding which occurred after puberty as distinguished from the other group of puberty bleeders which began practically with the first menstruation. In this group of thirty cases, fifteen were in the twenties, eleven were in the thirties, and only two were over forty. Sixteen patients were treated for only one cycle. Of these, eight had good results for six months or longer, one having recurrent metrorrhagia after six months. Half of these patients were also given thyroid therapy. Six of this group treated with one series of progesterone had recurrence of metrorrhagia within one to three months. Two were not followed for a sufficient period of time. It is to be noted that six of this group had minor metrorrhagia.

Two patients were treated for two months, each followed by withdrawal bleeding and controlled bleeding at the time, but they have not been followed sufficiently.

Twelve patients were treated for three months or longer. Actually three were treated for three months, four for four months, two for five months, one for six cycles, one for seven cycles and one for fourteen cycles. These treatments were not always consecutive but usually given for one to four months at the time. Of the three patients treated for three months, controlled bleeding without intermenstrual bleeding occurred but they have not been followed sufficiently to determine cure. Of the four patients treated for four cycles, three were cured and the fourth had a recurrence after five months. Two of these four were treated with thyroid. Two patients were treated for five cycles; one was cured over a prolonged period of time subsequently, and one has had an insufficient follow-up. One patient was treated for six cycles and later had a recurrence after five normal cycles. Thyroid was given to this patient. One patient was treated for seven cycles, and has been considered cured after prolonged follow-up. She is also taking thyroid. The last patient was treated for fourteen cycles intermittently. During the treatment, short series of normal cycles occurred followed by amenorrhea and recurrent metrorrhagia three separate times. No thyroid was given this patient. While this extensively studied case certainly has not been cured, bleeding has been controlled over a period of two years to her great satisfaction and with little abnormality.

In this group of thirty cases there were eighty-four treated cycles. Thirty-four were treated with progesterone, 10 mg. in oil intramuscularly daily for five days. There was no failure of withdrawal bleeding, the onset of which varied from one to eight days following the last injection, and in half the withdrawal bleeding began within two to three days after the last injection. There were six continuous withdrawals in which the hormone was given during the prolonged metrorrhagia. The bleeding stopped from one to five days after the last injection.

There were fourteen cycles treated with 50 mg. of progesterone in beeswax and peanut oil, given as one injection. There were seven normal withdrawal bleedings occurring in from three to eleven days. Two were three days later, two six days later, one eight days later, one ten days later, and one eleven days later. There were seven cycles of treatment given while bleeding was in progress, and the bleeding ceased from two to thirteen days later. It is to be noted that the withdrawal effects are more delayed after the beeswax, peanut oil preparation. In fact it is more prolonged than desirable.

There were nineteen courses of treatment given in miscellaneous manners, including 125 mg. in oil in one injection, 100 mg., 50 mg., in one injection, 25 mg. daily for five days, aqueous progesterone 20 mg. in one injection, and aqueous progesterone 60 mg. in one injection. Sixteen of these were followed by withdrawal bleeding in from one to nine days, the most prolonged being that following one injection of 60 mg. in aqueous suspension. There were three continuous withdrawal bleedings when the injections were given in the course of metrorrhagia. Satisfactory withdrawal effects followed all of these injections although in some the effects were delayed.

There were seventeen courses of treatment with sublingual progesterone. There were four failures following 30 and 50 mg. sublingually for five days. Withdrawal bleeding did occur in the remaining five cases with 30 mg. and 50 mg. sublingually for five days. Better results followed 100 mg. daily for five days, but in four instances the withdrawal bleeding was delayed for nine, twelve, and thirteen days, and three times was quite scant.

Endometrial studies before treatment showed interval nonsecretory endometrium or endometrial hyperplasia in nineteen patients. Biopsies were made

following eighteen courses of treatment. In five, normal-appearing late interval (early proggestational) or premenstrual endometrium was obtained. In five other cases, biopsies taken during bleeding showed typical fragmented menstruating endometrium as is seen in the normal menstrual phase. Four other cycles that were studied were labeled as follows: probable early secretion, hyperplasia background with some tendency to saw-tooth glands, subnuclear vacuoles in otherwise nonsecretory appearing endometrium, and slight secretion with interspersed hyperplastic glands. Biopsies made during bleeding after three other courses of treatment showed insufficient tissue, possibly indicating that the endometrium had been largely shed from the uterus. There was only one proved nonsecretory effect in the eighteen biopsies and this followed 100 mg. of progesterone sublingually for five days. While the effects of progesterone on the endometrium are not consistent in that all cases show the same degree of proggestational change, yet the vast majority do show some definite secretory changes in the endometrium, varying from a slight secretion with the hyperplasia background to the well-developed premenstrual endometrium, at times with decidua-like stroma, to the fragmented menstrual type of endometrium.

Hormone studies were made in some of the patients in this group. Seven patients had follicle-stimulating hormone studies which were all inconclusive. In one, tests were normal six times and high once. In the second, six tests were all normal. In the third, three tests showed once normal and twice high. In the fourth, one test showed too much (more than 85 mouse units per twenty-four hours). The fifth, with three tests, was normal. In the sixth, four tests showed one too high. In the seventh, three tests were above normal and one was normal.

Pregnandiol studies of the urines were made in a number of instances following progesterone administration. After progesterone, 10 mg. intramuscularly daily for five days, the level rose to 9.8 mg. in three days and dropped to 4.1. four days after the last injection. When progesterone, 50 mg. in beeswax and peanut oil, was given as one injection the level rose more slowly in two instances, one up to 20 mg. four days later and remaining at 8.9 mg. on the eighth day. Two other series showed very little rise (to 3.9 mg.). Progesterone, aqueous suspension 60 mg. in one injection, showed a delayed rise to 8 mg. on the fifth day with 4 mg. on the eighth day. Another series showed a rise to 9 mg. on the third day and 3.4 mg. on the fourth day. Progesterone, 20 mg. aqueous given daily for three days intramuscularly, showed a rise to only 3.3 mg. on the third day. Progesterone, 100 mg. in benzyl benzoate given in one injection, showed a rise the next day to 37.8 mg. Four days after the injection it was 7.2 mg. This suggested a remarkable increase in progesterone absorption. Eight courses of sublingual progesterone showed little or no effect after 20, 30, and 50 mg. daily sublingually but after 100 mg. daily the level rose after four days of treatment to 16.5 mg. and 47.6 mg. in two cases and on the eighth day of treatment to 13.8 mg. in the third case. While these tests are insufficient to be conclusive, they suggest that the administration of progesterone, 10 mg. in oil daily for five days, will maintain a rise over three or more days. In the beeswax and peanut oil a single injection may result in sustained rise even after eight days, which may explain the bleeding delayed for fifteen days in some instances. The aqueous progesterone was followed by a delayed rise for four days which probably explains why withdrawal bleeding usually follows this single type of injection. The sublingual administration of 100 mg. daily does show a remarkably high excretion of pregnandiol and may indicate that satisfactory results should follow this treatment, but it has not been studied sufficiently as yet.

One may conclude that progesterone therapy is exceedingly satisfactory in stopping bleeding in from three to ten days following the last administration of progesterone, and that withdrawal bleeding will occur, when no bleeding is

Results

From Table I, it is seen that the total group of 453 cases had an average IQ of 110.04 and personality rating of 2.27. In all groups except cesarean section, the children of primiparous mothers had a slightly higher IQ than those born of multiparas. Forceps and spontaneous deliveries resulted in a slightly lower IQ than breech, cesarean sections, and versions. (The small number of the three latter is probably misleading.) Of seven cesareans, only 2 patients were nontoxic, and the children of these two average the highest IQ in the entire series (126). All seven cesarean-born children have an average IQ of 114, which is higher than that following any other type of delivery. The personality ratings show the most favorable figures for cesarean sections, then spontaneous delivery, then breech, then version, and, last, forceps deliveries.

TABLE I

PERSON- ALITY RATING      IQ		PERSON- ALITY RATING      IQ		PERSON- ALITY RATING      IQ	
<i>Total Group, 453 Cases</i>		<i>147 Primiparas</i>		<i>294 Multiparas</i>	
	2.27    110.04		2.55    112.53		2.11    108.9
Male	2.26    108.2	Male	2.64    112.11	Male	1.91    106.26
Female	2.28    112.12	Female	2.15    112.70	Female	2.33    111.90
<i>380 Spontaneous Deliveries</i>		<i>107 Primiparas</i>		<i>265 Multiparas</i>	
	2.11    109.9		2.35    112.05		2.08    109.05
Male	2.05    108.21	Male	2.62    112.45	Male	1.74    106.55
Female	2.28    111.63	Female	2.11    111.67	Female	2.34    111.71
<i>49 Forceps Deliveries</i>		<i>31 Primiparas</i>		<i>14 Multiparas</i>	
	3.06    109.51		3.3    112.17		2.57    103.77
Male	3.32    107.91	Male	3.63    111.19	Male	2.68    101.5
Female	2.43    113.3	Female	2.44    114.47	Female	2.31    111.33
<i>13 Breech Deliveries</i>		<i>4 Primiparas</i>		<i>9 Multiparas</i>	
	2.45    112.85		2.75    124.25		2.32    107.11
Male	2.37    108.86	Male	3.7    136.	Male	2.15    104.33
Female	2.54    116.5	Female	2.43    120.3	Female	2.64    112.67
<i>7 Cesarean Births</i>		<i>3 Primiparas</i>		<i>4 Multiparas</i>	
	1.93    114.		2.13    104.		1.78    121.5
Male	2.23    110.7	Male	2.2    101.5	Male	2.3    129.
Female	1.7    116.5	Female	2.    109.	Female	1.6    119.
<i>2 cases (non-toxic cesareans)</i>					
	1.9    126.				
<i>4 Versions</i>		<i>2 Primiparas</i>		<i>2 Multiparas</i>	
	2.55    114		1.85    121.5		3.25    106.5
		Both female		Both male	

Personality rating: 1, superior; 2, above average; 3, average.

*Note:* In a few instances, parity was unknown; occasionally, sex also was not established from the records; these appear in the totals in the left-hand columns in these tables, but not in the subdivisions.)

Table II shows that eclamptic mothers have children with the lowest IQ in the entire series (101.2). This is more severe in primiparas than multiparas. Pre-eclampsia also results in a low IQ, but here multiparas are more affected than primiparas.

Only 13 children had jaundice as newborns; there is no drop in IQ, but the small number of cases may be misleading.

The effect of probable Pituitrin is striking. (The mothers were asked if they had received injections to hasten labor; the only other hypodermic injection these women were likely to have received in labor is morphine; hyoscine was not

in progress, on the average of three days later. It tends to be delayed after aqueous suspension, beeswax-peanut oil, and sublingual preparations. Of these thirty cases, thirteen have been considered cured. Seven of these patients had thyroid in addition. While cure may not always be expected with this method it does offer excellent control of bleeding, until nature may produce the reversion to normal. Secretory changes were produced in the endometrium in practically all cases treated in this series although there was variation in the response. It appears that the fragmentation that occurs in the endometrium during the normal menstrual cycle may be produced by progesterone. The changes from early secretory endometrium to the menstrual fragmentation may be very rapid in the course of two or three days' time.

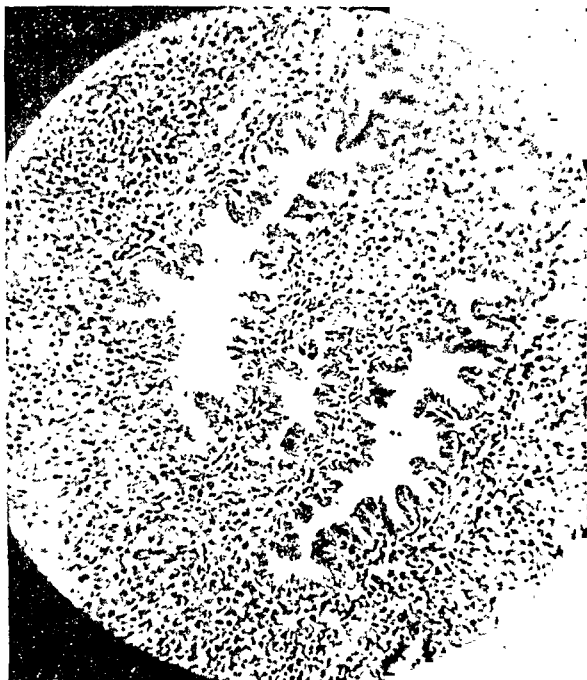


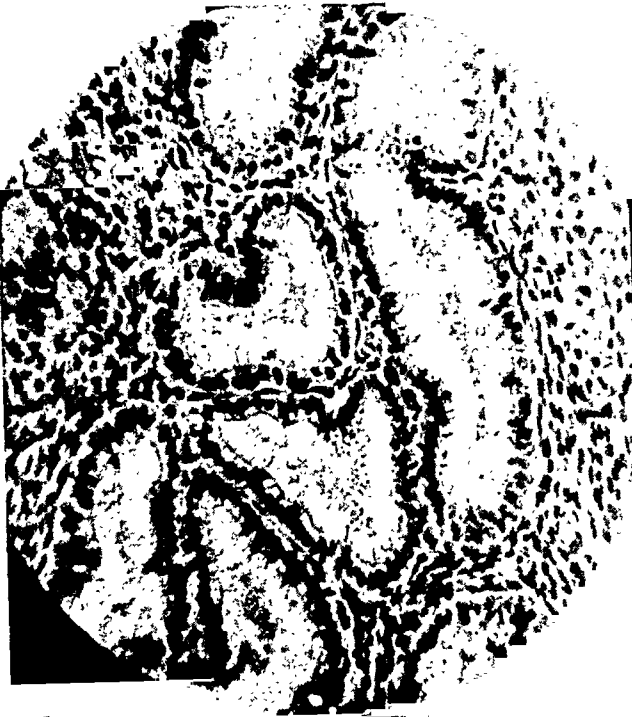
Fig. 12.—M. B., aged 26 years, metrorrhagia, endometrial hyperplasia. Progesterone, 100 mg. in benzyl benzoate for one injection. Biopsy seven days later, No. 48-1100. Pre-menstrual endometrium. Bled two days later.

### Primary Amenorrhea

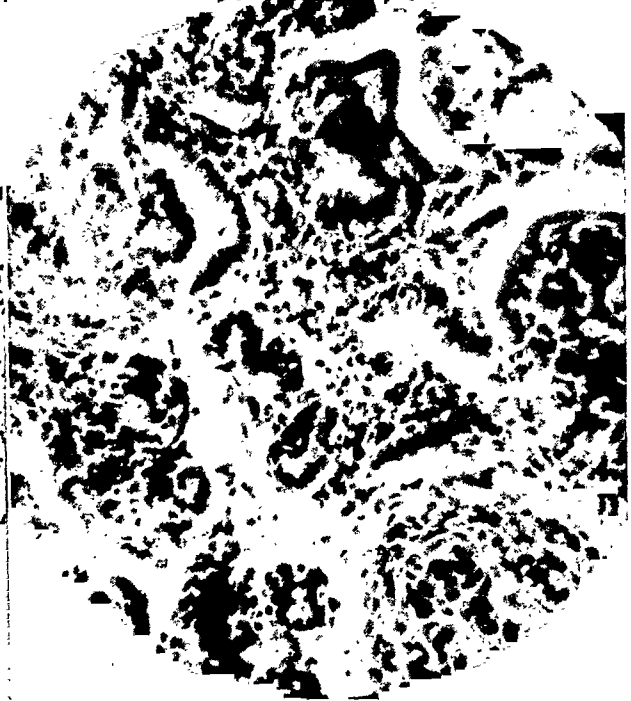
Seven patients with primary amenorrhea were studied. The ages were 17, 18, 19, 20, 23, 27, and 28 years. None had ever menstruated. Six showed thin vaginas and castrate smears. One (aged 17 years) had a thick vaginal mucosa with full estrogenic smear. Twenty-three courses of progesterone with added estrogen were given, followed by withdrawal bleeding sixteen times.

Six courses of progesterone 10 mg. with Urestrin, 10,000 I.U. (Cyclogesterin, Upjohn) daily for five days were followed by withdrawal bleeding five times and no bleeding once. Five courses with progesterone 12.5 mg. with estradiol benzoate 2.5 mg. (Prometron, Schering) daily for two days were followed by withdrawal bleeding three times and none twice. Aqueous suspension of progesterone 25 mg. with Urestrin 25,000 I.U. (Upjohn) for one dose produced bleeding once, for two doses produced no bleeding twice, for five doses produced bleeding once. Aqueous progesterone, 25 mg. for five doses, in a patient taking estrone sulfate continuously was followed by withdrawal bleeding once. In three patients primed with estrone sulfate (Premarin) withdrawal bleeding followed three times after progesterone, 50 mg. in beeswax-peanut oil.

8.



9.



10.

11.

Fig. 8.—M. F. C., aged 15 years, metrorrhagia, endometrial hyperplasia. Progesterone 125 mg. intramuscularly one day. Fourth day later, No. 47-1533. Late interval (early secretory) endometrium.

Fig. 9.—M. F. C., seventh day after progesterone (after Fig. 8). No. 47-1551, menstruating endometrium. Bleeding began.

Fig. 10.—M. F. C., progesterone, 20 mg. aqueous suspension intramuscularly every other day for three injections. Biopsy three days after last injection, No. 48-193, premenstrual endometrium. Bled two days later.

Fig. 11.—M. F. C., progesterone, 20 mg. aqueous suspension intramuscularly for one injection. Biopsy seven days later, No. 48-553, menstruating endometrium. Period began.

thirty-one patients were considered unimproved after treatment. Eight of these had received thyroid. Three of the seventeen subsequently developed progressive atrophy of the vagina and were thought entering an early menopause. Seven have been observed an insufficient time. Only eight patients have been considered improved or cured. One has become pregnant and five have been maintained on thyroid therapy. It is evident that progesterone alone will produce withdrawal bleeding, if absorbed over a period of three, four, or five days. Subsequently normal cyclic menstruation may follow in a minor percentage of cases.

### Comment

The above summaries illustrate the use of progesterone in the treatment of metrorrhagia and amenorrhea. It is evident that in the majority of these patients if an increased level of progesterone is maintained over a period of three or four days or more, a drop in the level will be followed by withdrawal bleeding, provided there is a moderately subnormal or higher level of estrogenic hormone present. If estrogens are absent, as in the true primary amenorrhea, no bleeding will follow. Also, the antibleeding effect of increasing levels of progesterone is useful in controlling prolonged bleeding in progress.

In this group of patients progesterone has been given in various forms in 278 courses. Continuous bleeding at the time the progesterone was given was followed twenty-one times by either cessation of bleeding on the third day and subsequent withdrawal bleeding three to five days later, or by continuous withdrawal bleeding for two to thirteen days. Delayed withdrawal bleeding at times followed progesterone, 50 mg. in beeswax-peanut oil or 60 mg. in aqueous suspensions. Added estrogens caused delayed bleeding in some cases. Evidently the beeswax and aqueous-suspension preparations may be too slowly absorbed and excreted for prompt decisive withdrawal bleeding. In only three instances was the first withdrawal bleeding unduly profuse, all aided by testosterone at the time, and one child received transfusions.

Expected withdrawal bleeding failed to appear after thirty-four series of treatments. Twenty-seven of the failures were in primary and secondary amenorrhea where a total of 141 series were given. Only seven failures were among the metrorrhagia groups. One received 125 mg. as one injection, and the absorption and excretion were undoubtedly too rapid. Six failures were after sublingual progesterone in doses of 50 mg. or less daily for five days.

Progesterone therapy is particularly applicable for control of metrorrhagia, especially in puberty bleeding. The most consistent results followed 10 mg. intramuscularly for five days, repeated at twenty-eight day intervals for three or four months. Various other forms listed above will produce satisfactory hemostasis and withdrawal bleeding, but the time intervals are not nearly as consistent. A single injection in oil is not satisfactory because of too rapid absorption and excretion. From beeswax-peanut oil, absorption is slow, results are satisfactory but the onset of withdrawal bleeding may be delayed an average of eight days, and occasionally as long as seventeen days. Following progesterone in aqueous suspension the results are frequently not as predictable. A product that will produce just the proper increase of progesterone for more than three days and less than six days is desirable for single injection medication. Aqueous progesterone is the nearest solution, although this particular product at times produces marked local pain. Certainly bleeding may be completely controlled and such control may be continued as long as necessary. It is realized that puberty metrorrhagia may last a few months or few years, but usually is spontaneously cured. This apparently innocuous therapy may be maintained as long as necessary. During this treatment anemia may be corrected, weight

Progesterone, 50 mg. in beeswax-peanut oil alone, and sublingual progesterone alone were followed by no bleeding. Sublingual progesterone, 100 mg. daily for five days, in a patient receiving Menagen (Parke, Davis & Co.) continuously had withdrawal bleeding twice. It seemed evident that these patients with primary amenorrhea and a thin vaginal mucosa must receive estrogen to prime the endometrium. Even then withdrawal bleeding was not constant.

Follicle-stimulating hormone assays were normal in two, and too high in two (more than 53 mouse units in twenty-four hours), suggesting that two were pituitary failures and two were ovarian deficiencies.

All seven patients received thyroid. Six with atrophic vaginas were not benefited except psychologically with the temporary bleeding. One (aged 17 years) with a thick vaginal membrane originally, continued to menstruate normally with thyroid, 2 grains daily. This patient probably should not be considered as having primary amenorrhea but delayed menarche.

### Secondary Amenorrhea

Thirty-one patients with secondary amenorrhea were treated with progesterone. The ages varied from 17 to 42 years. The majority were between 20 and 30 years. One hundred eighteen courses of progesterone were given, followed by withdrawal bleeding ninety-five times.

Various preparations and doses of progesterone were given. Ten mg. in oil intramuscularly daily for five days were followed by withdrawal bleeding after sixteen of eighteen courses, an average of three days after the last injection. The same dose with Urestrin added (Cyclogesterin, Upjohn) was followed by bleeding six out of seven courses, but was delayed three times for ten, eleven, and fourteen days. Progesterone, 12.5 mg. for two injections, with added estradiol benzoate 2.5 mg. (Prometron, Schering) produced bleeding after nineteen out of twenty-one courses, an average of three days later. Progesterone, 20 mg. aqueous suspension with Urestrin, 20,000 I.U., as one injection, was followed by bleeding sixteen out of seventeen times, varying from two to seventeen days later, averaging eight days. Progesterone, 25 mg. aqueous suspension with Urestrin 25,000 I.U. for two injections, was followed by bleeding thirteen out of fifteen times, from two to seventeen days later. Progesterone, 50 mg. in beeswax-peanut oil, was followed by withdrawal bleeding twelve of fifteen times, occurring three to ten days later, averaging five days. Progesterone, 125 mg. in oil as one injection (in 5 c.c.), was followed by normal bleeding once, scant bleeding once, and no bleeding twice. Progesterone, 50 mg. in benzyl benzoate daily for three days, was followed by bleeding two to four days later. Six failures of withdrawal bleeding followed sublingual progesterone given 25 to 50 mg. daily for five days. One hundred mg. sublingually were followed by withdrawal bleeding three times, one time scant.

Premenstrual or late interval secretory endometrium was found three times and nonsecretory endometrium once after progesterone, 10 mg. intramuscularly daily for five days. Progesterone, 50 mg. in beeswax-peanut oil, was followed by late interval secretory endometrium one time and insufficient tissue twice during bleeding, possibly meaning that the endometrium had been shed. After progesterone, 20 mg. aqueous suspension for two days, endometrial hyperplasia persisted in one case.

Follicle-stimulating hormone assays were normal in one case, low in one case (less than 6.6 mouse units) and high repeatedly in three cases (more than 53 mouse units).

Eight of the thirty-one patients showed slight atrophy of the vagina before treatment, but only one of these had no withdrawal bleeding after progesterone. The others were thought to have a normally thick vagina. Seventeen of the



25 and 30 mg. daily for five days, the findings were negative throughout or showed an occasional positive qualitative test. Two showed increases to 5 and 6 mg. on the third day. After 100 mg. daily sublingually, the pregnandiol rose on the third day of therapy to 10, 18, 6.3, 11, and 22 mg. in different cases. One increased to 36 mg. on the fourth day, 26 mg. on the seventh. Another increased to 34 mg. and 33 mg. on the fourth and fifth days. One patient who swallowed 100 mg. daily had a rise to 47 mg. on the fifth day. The injectable progesterone has seemed to give very slight rises in pregnandiol excretion, although apparently greater after beeswax-peanut oil and aqueous suspension preparations. The increases after the much larger doses given sublingually were remarkable and merit further study.

### Summary

1. Progesterone has been given in various forms as 278 courses of treatment in seventy-six patients.

2. Antibleeding effects during metrorrhagia and withdrawal bleeding effects have been utilized in controlling metrorrhagia and amenorrhea.

3. Of eight patients with puberty metrorrhagia, four were apparently cured, one had recurrence after six months, and one developed amenorrhea. Two were not cured, being controlled only as long as progesterone was given.

4. Of thirty cases with metrorrhagia after puberty, thirteen were considered cured (seven received thyroid).

5. Of seven patients with primary amenorrhea, one was cured. This patient had an estrogenic vaginal mucosa before treatment and probably had only delayed menarche.

6. Of thirty-one patients with secondary amenorrhea, eight have been considered improved or cured (five received thyroid).

7. Progesterone produces a menstruating type of endometrium with fragmentation and necrosis, which apparently clears the uterus of the superficial layers of endometrium.

8. This useful procedure controls bleeding accurately, but cure apparently depends on spontaneous reversion to normal, aided in some cases by correction of abnormal weight changes, and the administration of thyroid as indicated.

*Note:* The Endocrine Laboratory of the Department of Obstetrics and Gynecology of the University of Louisville Medical School has been aided for the past three years by generous grants from The Upjohn Company and Ayerst, McKenna and Harrison, Ltd. Progesterone has been supplied by The Upjohn Company, Ayerst, McKenna and Harrison, Ltd., E. R. Squibb & Sons, and the Schering Corporation.

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be regulated, and thyroid be given as indicated. It is possible that subsequent gonadotrophic therapy may be important under this control. There is no clear evidence from these clinical findings that progesterone stimulates pituitary function or indirectly produces ovulation.

In amenorrhea, therapy has been less satisfactory. In true primary amenorrhea there is no ovarian function and the patients are probably castrates at the start. Withdrawal bleeding occurred only if added estrogens were given, at least in small amounts. None of these patients with atrophic vaginas was cured. On the other hand, estrogens developed secondary sex characteristics and progesterone withdrawal bleeding was of psychological value. In secondary amenorrhea there is estrogen present, unless the patient has progressed to a premature menopause. Usually bleeding follows progesterone, in some cases estrogens must be added, but the results still are not consistent. After varied courses of treatments only eight of thirty cases with secondary amenorrhea were considered cured, and certainly thyroid therapy was an important factor in five.

Endometrial biopsies after progesterone showed secretory effects in twenty-seven series, insufficient tissue seven times during bleeding which may have indicated that most of the tissue had been shed, and no change in the nonsecretory endometrium seven times. Premenstrual or late interval secretory endometrium appeared quite normal thirteen times. Menstruating fragmenting endometrium was found eight times during bleeding on the first biopsy after treatment. Three showed quite early secretory changes as evidenced by subnuclear vacuoles in only part of the glands. Three showed a mixed late interval endometrium superimposed on a hyperplasia Swiss cheese background. Complete absence of secretion occurred in seven, after progesterone, 10 mg. intramuscularly for five days (two), progesterone 50 mg. in beeswax-peanut oil (one), progesterone 40 mg. in aqueous suspension (one), and progesterone sublingual 30, 50, and 100 mg. for five days (three). In contrast to the observations of others, secretory changes were common after progesterone therapy.

Menstruating-type endometrium with its marked fragmentation and necrosis, acute inflammatory cells, and disruption of glands lined by a single layer of cuboidal epithelium seemed a characteristic of progesterone bleeding. This is in contrast to the bleeding from relatively intact nonsecretory endometrium as seen in biopsies or the excised uterus. In one case this fragmenting endometrium was found on the sixth day after progesterone, 125 mg. intramuscularly. On the fourth day (two days previously) biopsy showed late interval secretory endometrium, such as is found about the twentieth day of the cycle. In another case nonsecretory endometrium preceded this fragmenting endometrium by three days. It seems likely that the diffuse fragmentation and necrosis of normal menstruation are caused by progesterone.

Hormone studies in this laboratory are not complete. References are made above to follicle-stimulating hormone determinations. The results were so variable that no conclusion is drawn. Pregnandiol studies have given some suggestions. The Guterman test for free pregnandiol was used throughout.

After 125 mg. in oil as one injection, the pregnandiol was 16, 5, 6, and 1.3 mg. on successive days. After 10 mg. in oil intramuscularly daily for five days, findings were negative qualitatively throughout or negative, negative, positive, negative, negative on successive days. After 50 mg. in beeswax-peanut oil, the pregnandiol rose to 3.9 and 4.5 mg. on the fourth day, but in one was 20 mg. on the fourth day and 9 mg. on the eighth. After aqueous progesterone 20 mg., negative results or very slight increases to 3 mg. were found. After 60 mg. aqueous suspension, there were rises to 8 and 9 mg. on the third and fifth days. After sublingual progesterone the pregnandiol recoveries were greater. After

be claimed. It is well known that endometrial hyperplasia is a manifestation of, often, only a self-limited intercurrent endocrine aberration which may be relieved spontaneously. Our own studies show no evidence of benefit to the underlying, probably pituitary factor which causes hyperestrinism from multiple follicular cyst development.

We are much interested at present in several cases under observation. The first was an instance of menometrorrhagia which had failed to respond to all accepted methods of therapy, including repeated curettage. Almost continuous menometrorrhagia since puberty was finally arrested by bilateral wedge-shaped resection of slightly enlarged microcystic ovaries. Since then, biphasic temperature patterns, pregnandiol excretion and—four months ago at the age of 28 years—the onset of pregnancy attest to the establishment of ovulation. In this instance microscopic sections of both ovaries failed to reveal any evidence of previous corpus luteum formation. We believe that ovulation had been inhibited by unopposed hyperestrinism which was relieved surgically by removal of the excessive follicular activity. We are awaiting further observations in the remaining cases before reaching conclusions.

DR. GEORGEANNA JONES, Baltimore, Md. (by invitation).—Dr. Te Linde and I have been interested in the treatment of menorrhagia with progesterone for a number of years.

I believe we are losing sight of the fact that Dr. Gray's paper is not concerned too much with the results of therapy, but with the more experimental aspects of the field. He was attempting to determine which was the best method of administration and what might be expected from the different methods of administration of progesterone, and also to give us some information as to the underlying histology of the therapy. I am very much interested in his histologic study; it has helped me considerably.

From a clinical point of view, I would say that in the past ten years we have treated seventy-two patients. These patients were confined to the menorrhagia group and represented only seventy-two out of 700 patients with functional bleeding seen in the clinic, which gives you some idea of the frequency with which this therapy is necessary. We used it only in severe cases, in patients who are young and desire pregnancies. In this group of seventy-two patients we have 18 per cent who became pregnant. Twenty of the patients apparently were cured by therapy with no other supportive type of treatment. Everyone knows that this condition does have remissions. However, our seventy-two patients were carefully selected as to endometrial patterns, and patients with medical conditions, inflammatory conditions, or tumors were excluded. We have had no failures in therapy in this group.

I think one difficulty in therapy is that sometimes the diagnosis is not properly made. One cannot expect to have good clinical results in patients who have complicating factors or in patients who have any suggestion of secretory endometrium or a regular cycle.

One must also understand the underlying histology which Dr. Gray has shown so well. Progesterone is not hemostatic; it does not stop bleeding but only controls it in a physiologic way when given in a cyclic manner. Sometimes bleeding does not stop until seven days after withdrawal of progesterone.

DR. EMIL NOVAK, Baltimore, Md.—The fundamental disorder in most of these cases of functional bleeding and, I believe, all of the group which Dr. Gray has so intelligently discussed, is a failure of ovulation. The curative treatment would be to make the patient ovulate, but here we meet with the same difficulties encountered in trying to induce ovulation in women who are infertile because they do not ovulate. Almost all the endocrine treatments of functional bleeding which have been recommended are make-shifts in that they are surface treatments, often purely hemostatic. This, I think, is true of what I believe to be the most effective hemostatic treatment of all in functional bleeding, that with estrogens. Such treatments control the bleeding, but do not usually cure the underlying pituitary disorder. The later occurrence of ovulation is likely really to cure the patient, but this is probably more often spontaneous than endocrine-induced. Dr. Gray has

## Discussion

DR. CARL P. HUBER, Indianapolis, Ind.—The management of functional uterine bleeding and amenorrhea has been the source of so much confusion in past years that every contribution which gives us additional controlled information is welcome. Quite obviously the method of therapy presented today is not the final answer. There were a considerable number of failures in all age groups. Definite conclusions cannot be drawn concerning dosage, method of administration, or predictability of results. This is equally true of other methods of treatment which have been suggested.

At the present time several plans of management for menometrorrhagia are in vogue and each has ardent advocates. Estrogens are used alone or in combination with progesterone. Androgens are used alone or also in combination with progesterone. In the present presentation, progesterone is used alone. In the light of our present knowledge of ovarian physiology a reasonable explanation can be given for each. Bleeding will temporarily cease following treatment according to any one of these plans but recurrences are frequent and upon occasion more radical methods become necessary. Nearly all support the additional use of thyroid where hypometabolism is present.

The author presents evidence to support the idea that the administration of progesterone in sufficient effective doses results in a more nearly normal menstrual slough of the endometrium than that which follows other types of therapy. This same pattern is seen when progesterone is used in combination with either estrogenic or adrogenic substances. He is to be complimented upon the effectiveness of his slides in demonstrating this point. This observation might suggest that where progesterone is used a more nearly physiologic result is obtained.

It remains important to emphasize that many patients with functional bleeding, perhaps 50 per cent, manifest spontaneous remissions and actually require no treatment. Such remissions may be induced also by curettage. Therapy which does not result in a higher cure rate has little to justify itself except perhaps a quicker control of bleeding. It may in addition be important to emphasize that, in the older age group, medical curettage should never supplant surgical curettage.

DR. FRANKLIN L. PAYNE, Philadelphia, Pa.—Briefly and to the point, I am a little disturbed over the thirty older patients who were treated as cases of dysfunctional bleeding, not having heard that all of them had the benefit of a thorough diagnostic curettage under anesthesia before treatment was instituted. I hope the essayist will reassure us on that point.

DR. HAROLD BACK, Detroit, Mich. (by invitation).—One must commend the essayist's honesty in presenting not only his successes but also his failures in attempting to induce menstruation (in the true sense of the word) from the atrophic endometrium of amenorrhea and endometrial hyperplasia as observed in instances of menometrorrhagia.

Our own experience with attempted replacement therapy in such instances of failure of ovulation are similar. As has been shown repeatedly, withdrawal bleeding can be induced in amenorrhea almost at will by estrogen or estrogen in combination with progesterone. Our studies of concomitant basal temperature determinations and pregnandiol excretion have, however, not shown any evidence of permanent curative effect from this form of therapy. Even though artificial basal temperature rises could be induced by progesterone, no evidence of ovulation could be established during or after such therapy. In several instances of secondary amenorrhea, spontaneous ovulation occurred at later dates quite independently, we believe, of our therapeutic efforts. Whatever benefits might be ascribed to such artificially induced, so-called menstruation has, we believe, purely psychic value with the additional advantage of demonstrating that the end organ is still capable of responding to suitable stimulation.

In menometrorrhagia, associated as it often is with cystic glandular hyperplasia of the endometrium, the benefit of temporary hemostasis and more orderly withdrawal bleeding is often of value. However, we believe that here too no definite curative effect can

## Original Communications

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### STUDIES ON PREVENTIVE AND CURATIVE TREATMENTS FOR Rh SENSITIZATION\*

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THE most recent and one of the most important advances in connection with blood transfusion is the discovery of the Rh factor. Knowledge concerning this has accumulated by leaps and bounds, and it has been necessary from time to time to revise our thinking. This, coupled with the fact that the subject is a complicated one, has led on occasion to some confusion. The essential nature of the Rh factor and its clinical applications are readily understood, if we avoid laboratory details and approach the subject from a broader and more general point of view.

A number of characteristics or factors of red cells had been discovered, and in 1937 Landsteiner and Wiener added another to the list, namely the Rh factor. All these factors, A, B, N, M, P, as well as the Rh, fall in the same general category of antigens. Antigens, under certain circumstances, have the ability to stimulate the production of corresponding antibodies. If cells containing any of these characteristics are introduced into the circulation and the corresponding antibody exists, an antigen-antibody reaction takes place and the clinical picture of hemolysis results.

Rh antibodies are not found preformed but may appear as a result of active or passive sensitization. Active sensitization may develop following repeated intravenous or subcutaneous injections of Rh-positive blood into an Rh-negative individual or as the result of pregnancy and the escape of Rh-positive cells of the fetus into the circulation of an Rh-negative mother. Passive sensitization, on the other hand, occurs if antibodies from a sensitized mother pass through the placenta into the circulation of the fetus. This paper will be limited to a report of efforts to meet the problem of active sensitization by the Rh factor.

It was most natural after scientific data concerning the nature of the Rh factor and its method of operation had accumulated that investigators should dedicate themselves to the task of preventing and counteracting Rh sensitization. In the case of transfusion this is simple. Wiener and Peters<sup>1</sup> recognized that 90 per cent of the post-transfusion intragroup hemolytic reactions were due to Rh sensitization. Methods of cross-matching blood of the donor with that of the patient then in vogue do not in every case detect the presence of Rh antibodies which presumably may be present. These methods must be changed. As a result such hemolytic reactions can now be avoided.

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\*Read at the New York Academy of Medicine at a joint session of the Pediatric and Obstetrical Sections, Feb. 10, 1949.

†Director Blood and Plasma Bank, New York University-Bellevue Medical Center.

taken cognizance of these facts, since he groups his cases into those which were controlled and those which were cured. I believe it was Ambroise Paré who used to say, "I treated the patient, and God cured him." To adapt this thought to the subject of functional bleeding, we treat the patients, but most often God cures them.

DR. GRAY (Closing).—One point brought out must have a proper answer and that is Dr. Payne's question. We believe every woman with metrorrhagia after the age of twenty-five, or recurrent metrorrhagia in younger women, should be curetted under Pentothal in the hospital before hormone therapy is given.

On the other hand, patients with puberty metrorrhagia should not be curetted, since medical hormone therapy appears to control bleeding with accuracy.

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Mollison, P. L., and Cutbush, M.: Exchange Transfusion in Haemolytic Disease of the Newborn, *The Lancet*, page 522, Oct. 2, 1948.

Whether tissue damage in the newborn is a direct effect of the circulating anti-Rh antibodies, or an indirect effect of the hemolytic process, is uncertain. While many infants with damage to the liver and brain may fail to exhibit anemia, the apparently good blood count may be due to (a) the delayed effect of a physiologic transfusion from the placenta (only counts from the cord at birth are reliable), (b) a rapid rate of red cell regeneration which may mask a high rate of hemolysis (as shown in cell survival experiments or by the hyperbilirubinemia present). Moreover, infants dying or stillborn because of profound birth anemia may not have had time to develop kernicterus. These points make it possible that tissue damage is specially associated with rapid blood destruction. The authors do not feel that anti-Rh causes direct tissue damage, since they have sometimes noted large amounts of free Rh-antibody persisting for weeks with no evidence of progressive liver or brain damage.

It is doubtful that tissue damage is established at birth, and, insofar as it may be subsequent to the destruction of Rh-positive cells, substitution transfusion is prophylactic. While either a simple or a replacement transfusion removes the physiologic stimulus (anemia) to the formation of new Rh-positive cells, the former procedure preserves the initial load of Rh-positive cells for destruction and excretion. A second rationale for exchange transfusion is the rapid correction of a profound anemia without overloading the circulation.

The authors have performed thirty exchange transfusions by the umbilical vein. (Diamond, 1947.) A transparent plastic catheter is passed 2 to 3 inches, to the point where blood is freely withdrawn. Twenty c.c. exchange aliquots are used, and the apparatus being rinsed with dilute heparin-saline solution, occasionally. The total exchange is 300 to 450 c.c., sometimes followed by a 50 c.c. donor supplement. In most cases the exchange was done within thirteen hours of birth, but the procedure has also been successful up to 38 hours after birth. There were no cases of umbilical sepsis, air embolism, or other ill effect. Prophylactic doses of penicillin are recommended, although used in only 10 per cent of the cases here reported. If some supernatant plasma-citrate is removed from the donor blood, the improved donor hematocrit permits an improved absolute and proportionate Rh-negative cell count, whereas the number of residual Rh-positive cells depends only on the volume of blood exchanged.

Analysis of this series shows a mild course in infants whose cord blood contained more than 15 mg. of hemoglobin and less than 3 mg. of bilirubin, per 100 c.c. Infants having anemia and high bilirubin had a stormy or fatal course. The authors suggest that exchange transfusion be reserved for this latter group. Of the thirty infants treated, twenty-three survived, only one showing residual nervous system damage.

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used even in hospital deliveries at that time.) The drop is from 110.04 for the whole series to 105.11 in the probable Pituitrin group, and to 99.85 in the male multiparous births. Personality rates roughly follow the same pattern. The fast labors are a suspicious factor in lower IQ.

TABLE II. EFFECT OF TOXEMIA, JAUNDICE, AND PROBABLE PITUITRIN

PERSON-ALITY RATING IQ			PERSON-ALITY RATING IQ			PERSON-ALITY RATING IQ		
<i>Eclampsia 6 Cases</i>			<i>5 Primiparas</i>			<i>1 Multipara</i>		
	2.75	101.2		2.78	95.75		2.6	126.0
4 males	2.95	104.	3 males	3.07	94.5	1 male	2.6	126.0
2 females	2.35	97.	2 females	2.35	97.			
<i>41 Pre-eclampsia</i>			<i>13 Primiparas</i>			<i>27 Multiparas</i>		
	2.57	105.89		2.71	110.5		2.44	102.85
24 males	2.86	104.46	Males	3.43	110.43	Males	2.67	102.
17 females	2.03	108.9	Females	2.1	110.53	Females	2.98	105.7
<i>13 Jaundiced Babies</i>			<i>6 Primiparas</i>			<i>7 Multiparas</i>		
	2.51	112.27		2.53	120.4		2.5	105.5
8 males	2.85	114.	5 males	2.74	118.75	3 males	3.03	104.5
5 females	1.98	110.4	1 female	1.5	128.	4 females	2.1	106.
<i>62 Cases Probably Receiving Pituitrin</i>			<i>20 Primiparas</i>			<i>42 Multiparas</i>		
	2.54	105.11		2.3	111.4		2.64	102.18
Males	2.68	101.86	Males	2.34	106.89	Males	2.8	99.85
Females	2.41	108.68	Females	2.26	117.22	Females	2.49	104.63
<i>For Comparison: Entire Group (453)</i>			<i>147 Primiparas</i>			<i>294 Multiparas</i>		
	2.27	110.04		2.55	112.53		2.11	108.9
Males	2.26	108.2	Males	2.64	112.11	Males	1.91	106.26
Females	2.28	112.12	Females	2.15	112.7	Females	2.33	111.90

In Table III, chloroform deliveries are associated with a higher IQ than deliveries under ether. Chloroform being administered with more oxygen results in less anoxemia to the infant; the difference is more probably explained by the fact that most of the chloroform anesthetics were light and short, while most of the hospital deliveries were under almost surgical depth ether anesthesia. The final total anesthesia includes known ether and chloroform and cases where anesthesia must have been used due to the type of delivery (version and forceps), but no mention of the type of anesthesia was found. Personality rates are comparable to the IQ in the anesthesia group.

TABLE III. ANESTHESIA

PERSON-ALITY RATING IQ			PERSON-ALITY RATING IQ			PERSON-ALITY RATING IQ		
<i>123 Chloroform</i>			<i>39 Primiparas</i>			<i>84 Multiparas</i>		
	2.39	111.72		2.25	115.61		2.47	109.77
Male	2.57	110.59	Male	2.29	115.77	Male	2.77	107.6
Female	2.21	113.2	Female	2.14	116.56	Female	2.24	111.84
<i>33 Ether</i>			<i>18 Primiparas</i>			<i>15 Multiparas</i>		
	2.45	107.67		2.51	101.2		2.37	114.13
Male	2.8	103.78	Male	2.64	98.3	Male	3.	110.78
Female	2	113.5	Female	2.34	107.85	Female	1.66	119.17
<i>179 Total Anesthesia</i>			<i>72 Primiparas</i>			<i>107 Multiparas</i>		
	2.4	111.08		2.37	112.26		2.42	110.18
Male	2.62	108.91	Male	2.49	110.58	Male	2.71	107.59
Female	2.16	113.92	Female	2.2	115.7	Female	2.13	112.93

New rules have been established for the selection of donors for transfusion. Rh-positive blood should be given to all Rh-positive patients, except to newborn infants with erythroblastosis due to Rh sensitization. To these only Rh-negative blood should be transfused, even though the infant necessarily is Rh positive. Only Rh-negative blood should be given to all Rh-negative females from birth to the climacteric, otherwise sensitization by the Rh factor might follow and interfere with normal pregnancy. For Rh-negative females after the climacteric and for Rh-negative males of any age Rh-positive blood may be given when necessary providing it is recognized that as a result Rh antibodies may develop, and providing subsequently the proper pretransfusion tests are performed.<sup>2</sup> If sensitization results, for all subsequent transfusions only Rh-negative donors may be used. It must also be remembered that even when Rh-positive blood is used exclusively for Rh-positive patients the possibility of sensitization by the *rh'* or *rh''* factors may also occur.<sup>3</sup> This can always be avoided if a donor is selected whose Rh *type* is identical with that of the patient. The mere presence of Rh antibodies in the serum of an Rh-negative individual is inconsequential to that person unless pregnancy develops or unless transfusion is required.

Our experience has shown that while the frequency of Rh-negative individuals in the general population is about 15 per cent, demands for this type of blood for transfusion run as high as 25 and 30 per cent, and at one institution this has reached 100 per cent. This is due to the use of donors with Rh-negative blood as universal donors when preliminary Rh testing has actually been omitted. This should be condemned. The successful operation of any bank will be defeated if patients not requiring Rh-negative blood are given this variety, and if then those who genuinely require it are deprived of it. In addition it must be recognized that sensitization to the Hr factor may develop as a result of this practice and this too can interfere with a successful pregnancy.

The second circumstance during which active sensitization by the Rh factor may become apparent is during pregnancy. Levine, Burnham and Katzin<sup>4</sup> showed the relationship between erythroblastosis and atypical agglutinins in the mother's serum. Levine and his co-workers established the fact that at least 90 per cent of cases of erythroblastosis fetalis were due to Rh sensitization. Bloods of such mothers show the presence of Rh antibodies. Coping with the problem of sensitization due to pregnancy is not as simple as the similar problem with transfusion.

Three methods of treating the mother have been studied: (1) repeated partial replacement transfusions, (2) countersensitization with bacterial vaccines, and (3) treatment with haptens. Replacement transfusions are not really as new as they sound. As far back as 1917<sup>5</sup> I published my experience with an attempt to affect the course of leucemia and pernicious anemia by replacement transfusion. Recently the method has been revised. It is now used for newborn infants with erythroblastosis. Bessis of Paris is also using it for treatment of leucemia and other conditions.

It seemed reasonable that repeated partial replacement transfusions might possibly reduce the titer of antibodies in blood of a mother sensitized by the Rh factor, or at least prevent a rise. Under such circumstances a case which otherwise would be severe or even fatal might conceivably be converted into a mild one and the infant recover. To test this method four cases were treated in this fashion. All of these women had typical marital histories. They all showed Rh antibodies in their sera; two had anti-Rh agglutinins and two had Rh blocking antibodies. In one case saline agglutinins were present in a titer of 256, and in another the albumin-plasma conglutination test gave a titer of 2048. One patient was an interim case, while the other three were pregnant at the time of treatment. In each case 500 c.c. of blood were withdrawn and 500 c.c. transfused and this process repeated until the total amount previously decided upon



had been removed and replaced. In one case 6,500 c.c. were replaced over a period of twenty and one-half weeks (Fig. 1); in the second case 6,500 c.c. in eleven and one-half weeks (Fig. 2); in the third case 8,500 c.c. in nine and one-half weeks (Fig. 3); and in the fourth case 21,000 c.c. in fourteen and one-half weeks (Fig. 4). In this last case 10,000 c.c. were removed and replaced at only three sittings over a period of four days.

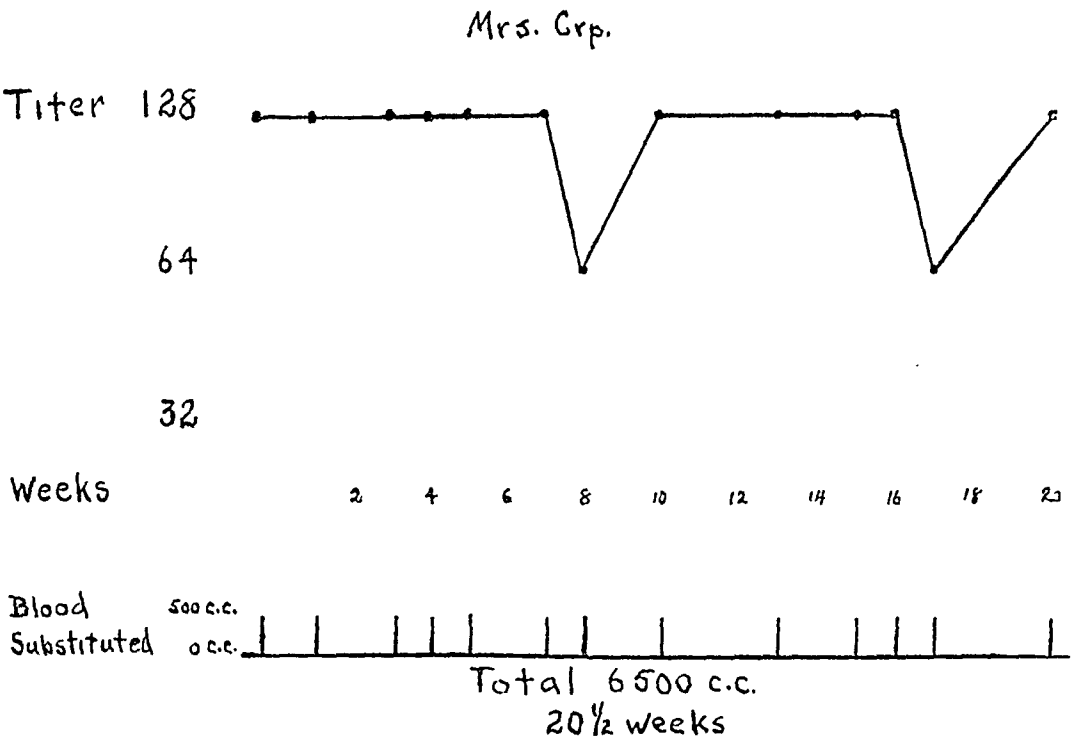


Fig. 1.—Results of antibody titrations (albumin-plasma conglutination technique) during pregnancy in Case 1 treated with replacement transfusions. Cesarean, erythroblastotic infant.

The bloods of all patients reported in this paper were examined not only for agglutinins using saline medium, and for blocking antibodies using the indirect test, but also for antibodies using albumin-plasma medium. The illustrations throughout indicate titers obtained when the latter medium was employed. It must be remembered that a difference of one dilution between any two sets of successive titer readings, for example, the difference between 512 and 256, is of no greater significance than the difference between 2 and 1. Therefore, a scale of titers on an arithmetic rather than a geometric basis grossly exaggerates the significance of fluctuations at the upper level of the scale and is misleading. In all charts depicted in this paper the geometric scale has been used.

Figs. 1 to 4 give the results of antibody titrations in the cases where replacement transfusion was used. Because of the limitations of the test there can be a difference in the results of two successive tests of one or two dilutions which should not be interpreted as necessarily significant. If, however, repeated subsequent tests show a continuation of this downward or upward trend, the difference does become definitely significant. Although the trend in two of these cases was possibly slightly downward, in neither was it sufficiently marked to be certain that these changes were due to treatment rather than to limitations of the test.

In the first case (Fig. 1) where the titer remained unchanged throughout pregnancy, a previous pregnancy had resulted in an erythroblastotic infant who died. The present pregnancy was terminated by cesarean section after thirty-

three weeks. The infant, who was Rh-positive, was immediately given a partial replacement transfusion and made a perfect recovery. At no time was jaundice evidenced. The child is living and well and is now 1 year old. The second case (Fig. 2) was an interim case. The third patient (Fig. 3) gave birth to a 7½-month erythroblastotic infant who died within a matter of hours. The fourth patient (Fig. 4) gave birth prematurely to an Rh-negative infant who soon died.

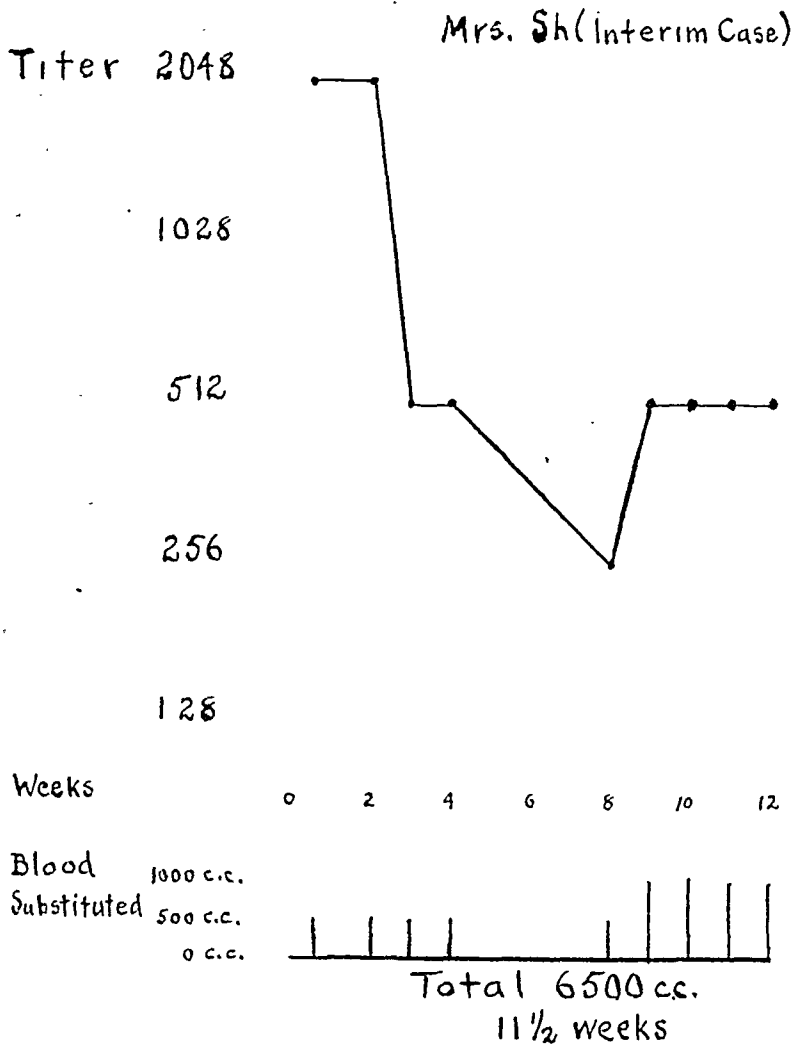


Fig. 2.—Results of antibody titrations (albumin-plasma conglutination, technique) in Case 2 (not pregnant) treated with replacement transfusions.

Of course, at the outset it was fully recognized that antibodies are not only present in the circulating blood of the mother, but also that the tissues are saturated with them and that the expected results might not materialize. Beside this reserve, it is likewise possible that the rate of new production is so rapid that no appreciable reduction in titer may be observed. Perhaps the amounts of blood removed and replaced should be greater. Possibly twenty or thirty liters over the period of a week might be more effective. At present, however, I am forced to conclude that this mode of therapy in the doses used has little if any ability to reduce the titer of Rh antibodies. An additional drawback is the fact that huge amounts of Rh-negative blood are needed to carry it out. This is expensive and it might be difficult in certain localities to obtain such large amounts at a time because the patient may not be near a very large blood bank.

The second mode of therapy undertaken was that of countersensitization. As previously stated the Rh factor is an antigen. Under certain circumstances

an Rh-negative mother may develop antibodies of a specificity corresponding to that of the Rh factor inherited by her infant. The mechanism is one of antibody response to stimulation by an antigen and is identical in principle with the reaction to any other antigen.

Landsteiner<sup>6</sup> pointed out that specific substances have been seen to interfere with each other in their antigenic action, e.g., the highly active Forssman substance may inhibit the formation of antibodies against other specific substances. This interference, German writers have termed *Konkurrenz der Antigene* (competition of antigens).

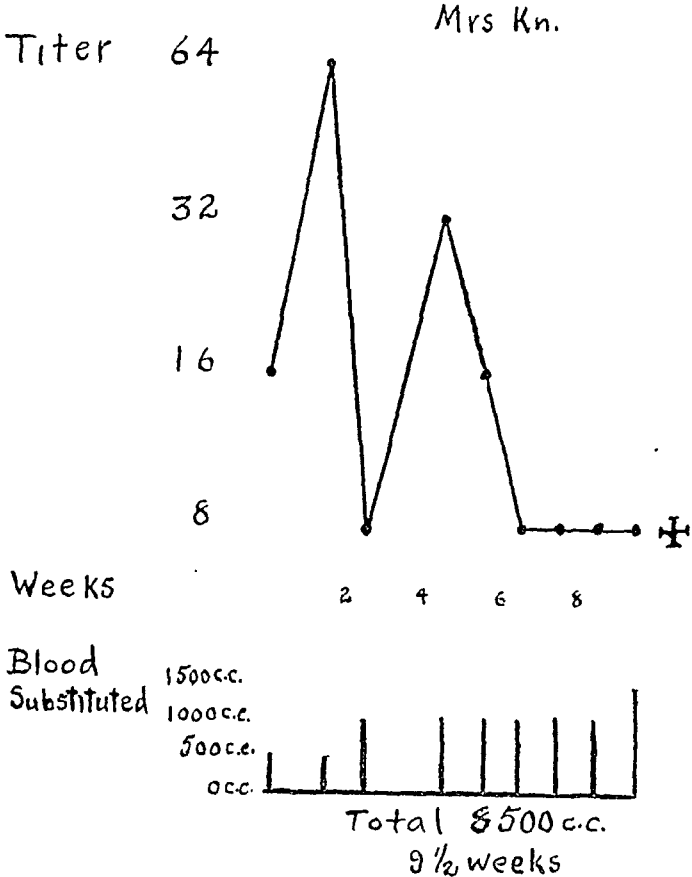


Fig. 3.—Results of antibody titrations (albumin-plasma conglutination technique) in Case 3 treated with replacement transfusions. Premature infant, erythroblastotic.

Workers in the problem of protection against viruses have had similar experiences and refer to the effect as an “interference phenomenon.” Andrews<sup>7</sup> states that the existence of one virus in the host sometimes prevents an attack by a second virus, and the two viruses need not be antigenically related.

Another illustration of the phenomenon of competition of antigens is in connection with the use of diphtheria toxoid which contains not only diphtheria antigen, but also A substance obtained from pig stomach used for preparation of peptone necessary for production of toxoid. Therefore, when such toxoid is administered to a patient, two antigens are simultaneously injected. If the blood of the patient happens to belong to group A naturally he cannot respond to A substance and can only respond to toxoid. If he should belong to group B he is in a position to respond to both antigens and competition between the two ensue and he usually responds only to the more potent, namely, the A substance. This is supported by the findings of Tomaki and others who showed that im-

munization against diphtheria is more successful in Group A than in Group B individuals.

Additional evidence is found in a study of the incidence of Rh sensitization in pregnancy. If the mother is Rh negative, and the fetus is Rh positive, but in addition the ABO group of both mother and child are identical, only a single incompatibility exists. If in addition to the Rh incompatibility there is an ABO incompatibility, a double incompatibility exists. Both mothers may have been exposed to the identical Rh antigen, yet the incidence of Rh sensitization in these two groups of pregnancies differs. According to Diamond (personal communication) if the husband is homozygous and there is a single incompatibility, the incidence of sensitization is 11 per cent, whereas if there is a double incompatibility, the incidence of sensitization is reduced to 4 or 5 per cent.

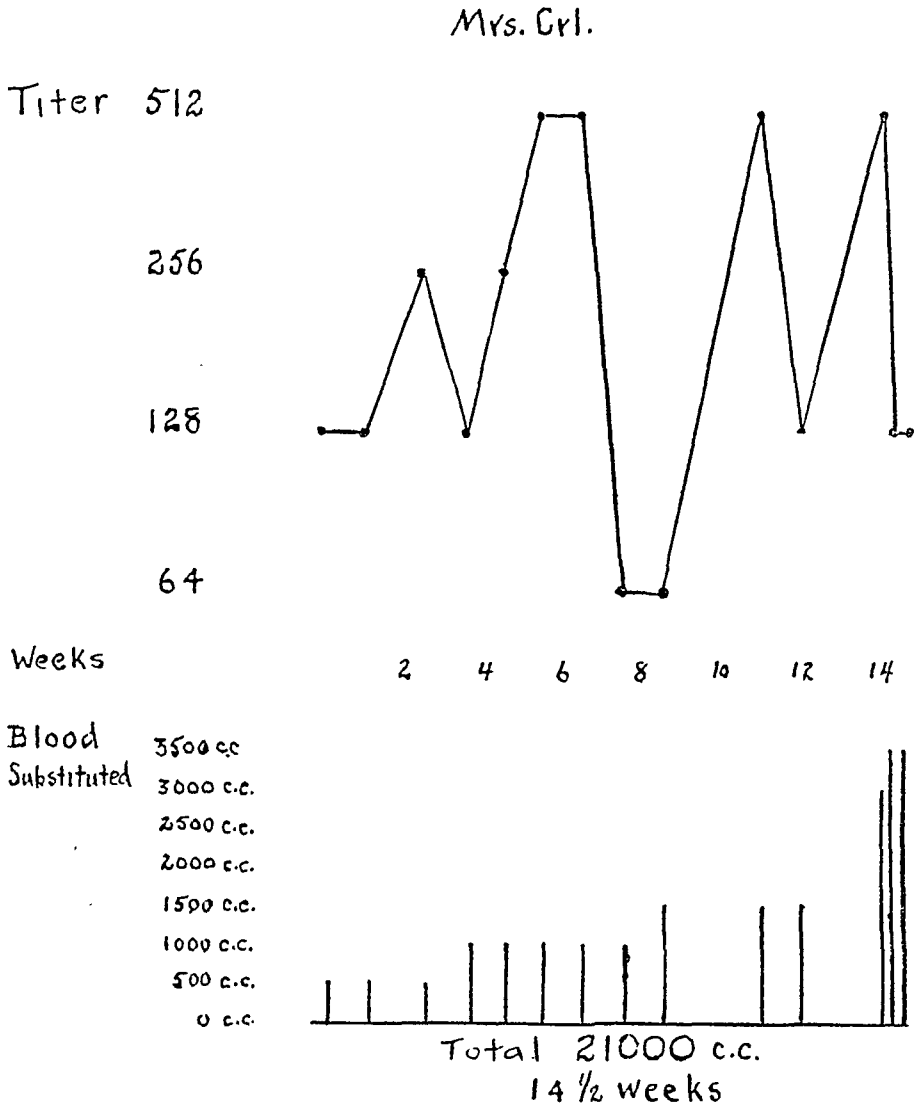


Fig. 4.—Results of antibody titrations (albumin-plasma conglutination technique) in Case 4 treated with replacement transfusions.

Under similar conditions with a heterozygous husband and a single incompatibility, the incidence is 3 per cent, whereas with a double incompatibility it is reduced to 1 per cent. Levine,<sup>8</sup> Wiener,<sup>9</sup> as well as Race<sup>10</sup> and his co-workers have also made similar observations. A plausible explanation for these findings is that with a double incompatibility the A or B factor is in competition with the Rh factor. The A and B factors are more antigenic than Rh, and the

mother tends to respond to them with greater ease than to the Rh factor which is then ignored.

Competition of antigens is merely a special situation illustrating a general physiologic phenomenon; namely, that a strong stimulus tends to suppress a weak one. It is difficult to hear a whisper in a boiler factory, or to detect faint odors in the presence of stronger odors, or to feel deeper seated pain when counterirritation is applied. This does not mean that the body is incapable of responding to more than one stimulus or one antigen at the same time, but merely that injection of a strong antigen *tends* to suppress the antigenicity of a weaker one injected at the same time. For competition of antigens to operate, correct "timing" is of utmost importance. To use a prosaic example, a loud noise today cannot overwhelm a whisper uttered tomorrow. Similarly, if the two antigens are not present in the individual at the same time, they can hardly compete with one another. Under natural conditions, when there is a passage of fetal blood into the maternal circulation, the same blood cells carry A and B antigens as well as Rh antigen so that in this instance timing is perfect, and interference results.

There is much evidence to support the theory of competition of antigens. Wiener<sup>11</sup> was the first to suggest that this phenomenon might be put to practical use and result in protection of Rh-negative women carrying Rh-positive fetuses, and that innocuous antigens such as typhoid and pertussis vaccines can be used to suppress the antigenicity of the Rh factor. There have been differences of opinion on the subject, yet none has been based on a large practical trial. The subject seemed to be of such great importance that a systematic study was undertaken. Methods for the production of diagnostic sera offered an opportunity to test the theory. At first diagnostic sera for Rh studies were prepared by artificial sensitization of animals. This for many reasons was unsatisfactory. Subsequently, sera obtained from mothers of erythroblastotic infants were used for this purpose. However, demand for diagnostic sera became so great that more recently workers in this field have obtained diagnostic serum from volunteer male professional donors injected with Rh-positive blood. Of a group of nine injected donors reported by Wiener and Gordon<sup>12</sup> five, or 55 per cent, responded with the production of Rh antibodies. Wiener also states in a personal communication that he has now increased this group to forty-seven. Of these, 38.3 per cent developed antibodies after the second injection. Twenty-three of the remainder received a third injection of Rh-positive cells and six developed antibodies. The cumulative total per cent sensitized, therefore, after two or three injections, was 54.4 per cent. This is further supported by a report of Diamond who states that in a group of 380 male Rh-negative veterans given Rh-positive blood transfusions, 53 per cent developed Rh antibodies. By reproducing Wiener's exact procedure, but with the addition of vaccine therapy, Wiener's series of injected donors could be used as my control series. This offered the opportunity to determine the preventive value of countersensitization. The program was planned to simulate first, second, and even third pregnancies, during which vaccine was administered. Of seven injected Rh-negative men only one developed antibodies, an incidence of about 14 per cent (Table I) instead of the expected 54.4 per cent. It is fully recognized that conclusions based on small numbers might be erroneous and that absolute safety is found only in very large numbers. Yet large numbers in a test of this sort are from a practical standpoint difficult of attainment and hardly feasible. At any rate the results certainly are very suggestive. Another observation is that the only individual of this group who did develop Rh antibodies showed a negative Widal to the O antigen although positive to the H antigen, whereas all other donors injected with typhoid vaccine who developed no Rh antibodies responded positively to both typhoid antigens.

TABLE I. OBSERVATIONS ON Rh SENSITIZATION IN Rh-NEGATIVE MALES WITH AND WITHOUT COUNTERSENSITIZING VACCINE INJECTIONS

INVESTIGATOR	COUNTERSENSITIZATION	NUMBER OF INJECTIONS OF Rh-POSITIVE CELLS	NUMBER OF SUBJECTS	FREQUENCY OF Rh ANTIBODY FORMATION		CUMULATIVE TOTAL (PER CENT) SENSITIZED
				NUMBER	PER CENT	
Present study	Typhoid and pertussis vaccine used	2	7	1	14	14
		3	5	0	0	14
Wiener* (control series)	None used	2	47	18	38.3	38.3
		3	23	6	26.1	54.4

\*Proc. Soc. Exper. Biol. &amp; Med. 70: 576, 1949.

Van Loghem<sup>13</sup> of Holland has reported the results of Rh sensitization of volunteer donors. He believed that the injection of vaccine simultaneously with exposure to the Rh factor will increase the incidence of those who produce Rh antibodies. His conclusions, however, are open to question, because his donors received numerous injections of Rh-positive cells without vaccine, and then later received repeated injections (totaling up to sixty and more) of Rh-positive cells and only a few injections of vaccine. His donors first had been "primed" by the Rh antigen and then later given stimulating doses of Rh-positive cells. Even then, his incidence of sensitization was 21 per cent which is much lower than the expected 54.4 per cent. His technique was entirely different from the one followed in this present test and, therefore, his results and those of this study are not comparable. In my series, as well as in Wiener's, between each injection of cells there was an interval of 90 or more days, and the technique followed in both investigations was identical in every respect except that in my series weekly injections of vaccine (totaling twenty-one to twenty-seven) were administered to prevent Rh sensitization.

Another possibility that has been claimed is that of nonspecific response. It has been suggested that if an individual has already been "primed" by the Rh factor, subsequent injections of vaccine might stimulate the production of Rh antibodies.

Because of the experimental evidence supporting the theory of competition of antigens, and because of the lack of danger in connection with the use of typhoid and pertussis vaccines, and because any immunity developed by the mother would be of value to the infant, a clinical trial was begun two years ago.\* The following program is now being carried out in the outpatient Obstetrical Department of St. Clare's Hospital.† Rh typing is performed on the blood of every expectant mother. In other words, her blood is examined not only for the Rh<sub>0</sub>, but also for the rh', rh'' and hr' factors. In addition an ABO grouping, and M and N typing is made. If the mother is found to be Rh negative, whenever it is possible to obtain blood of the patient's husband, similar examinations are made. If these tests reveal that the possibility of sensitization exists, counter-sensitization is begun. Typhoid vaccine 1,000 million per cubic centimeter and pertussis vaccine 20,000 million per cubic centimeter furnished by the Department of Health of the City of New York are used. Until pregnancy is terminated alternating series of six weekly injections of each of these vaccines are given. The dose is gradually increased at the beginning of each series. If an injection is followed by a reaction, the subsequent dose is cut in half. Monthly, up to the seventh month, examinations for anti-Rh agglutinins and Rh blocking antibodies are made. During the seventh month this is done twice and then once a week

\*These cases were kindly referred to me by Dr. Locke Mackenzie.

†The opportunity to introduce this program was kindly afforded me by Dr. Michael Jordan, the attending obstetrician.

until the end of pregnancy. An Rh typing is done on the cord blood of the newborn infant. It is also examined for antibodies and coating of the cells. Since this program entails a terrific amount of work and cooperation, it was not always possible to carry out every detail as outlined. At the obstetrical clinic of Woman's Hospital I have introduced a similar program, except that no vaccine is being given. This might be used as a control group, except that the two groups of patients are racially different.

Up to the present we have treated or are still treating by countersensitization ninety-three Rh-negative women (Table II). Even though it is recognized that the first pregnancy is practically always spared, twenty-six of the group who were primiparas were also given treatment because of the importance of "priming." It is felt that they should be "primed" against the bacterial antigen before they have the opportunity to be "primed" against the Rh antigen, thus making certain that the vaccine is the more potent antigen. It also seems important that these primiparas be given an injection of vaccine at the time of delivery when the likelihood of leakage of Rh-positive cells from the fetus is probably greatest. It is hoped that they will return at the time of their second pregnancy so that this thesis can be tested. Fifty-eight of the patients were multiparas. Of the entire group, one patient, in spite of countersensitization, developed Rh antibodies. Peculiarly enough her Wassermann was four plus. The significance of this is unknown. After the birth of her infant a partial replacement transfusion was performed. A mild degree of jaundice developed. However, the child recovered without any further treatment and is now living and well.

TABLE II. OBSERVATIONS ON Rh SENSITIZATION DURING PREGNANCY IN Rh-NEGATIVE PATIENTS RECEIVING COUNTERSENSITIZING VACCINE INJECTIONS

	NUMBER OF Rh-NEGATIVE WOMEN TREATED	RESULTS OF PREGNANCY			
		STILL- BIRTH	ERYTHROBLASTOSIS		NORMAL
			DIED	RECOVERED	
Nonsensitized primiparas	26*	0	0	0	25
Nonsensitized multiparas	58†	0	0	1	40
Previously sensitized multiparas	9	5	1	3	0

\*One of these pregnancies is not yet terminated.

†Seventeen of these pregnancies are not yet terminated.

Nine women who had been sensitized by previous pregnancies were also treated. This practice has now been discontinued. Our experience shows that vaccine therapy in such women is of no avail. If the value of vaccine therapy can definitely be established it will be as a *preventive* measure for those who still show no evidence of sensitization. Although it is felt that sufficient evidence has accumulated to warrant the belief that this form of therapy may possibly prove to be of value to reduce the incidence of sensitization to the Rh factor, it is definitely not infallible. It is also fully recognized that it will take experience of several years more before a final appraisal of this prophylactic treatment can be given. In making use of this therapy one must keep in mind the necessity for proper "priming" and proper "timing," otherwise failures will result. "Priming" is necessary to insure the greater potency for the vaccine as compared to the Rh factor. "Timing" is necessary to develop competition between them. If a patient has previously been sensitized by the Rh factor, it may have become a more potent antigen than the vaccine. The vaccine treatment must be continuous throughout pregnancy. Perhaps some other antigen will be developed or used which can be given less frequently, and that it will be so retained by the patient that the effect will be more continuous and solve the problem of

"timing." That such vaccines may be feasible follows from experimental work of Freund and his co-workers<sup>14</sup> on bacterial vaccines suspended in oil of light viscosity.

It will probably take several years before the final word on this subject is spoken, especially if only one or two investigators carry out the work. This is true because only a small percentage of women in whom the potentialities for sensitization exist become sensitized. I estimate that it will be necessary to observe at least approximately 10,000 consecutive pregnancies to arrive at a final answer. Perhaps even double this number may be necessary. If this method of treatment then shows a definite reduction in the incidence of erythroblastosis, a final conclusion could be arrived at. Obviously this would be a colossal undertaking. It is suggested, therefore, that this treatment be undertaken by other clinics and that results be pooled and evaluated. It is only in this way that we can more quickly come to a definite decision. It is necessary to have very large numbers of cases treated in order finally to say exactly what role the treatment has played in the reduction of the incidence of erythroblastosis fetalis.

The third method of approach studied was the use of a new substance, the so-called hapten. The term hapten was introduced by Landsteiner to designate materials capable of reacting specifically with antibodies in vitro, but incapable themselves of stimulating the production of antibodies when injected into experimental animals. Rh hapten is intended for treatment of women whose blood shows the presence of Rh antibodies and for treatment of infants with erythroblastosis.

In 1944 Wiener<sup>15</sup> suggested the possible value of hapten. More recently Carter<sup>16</sup> produced hapten and used it clinically. This substance she obtains from an ethereal extract of Rh-positive cells which is next reduced to dryness, and the residue dissolved in alcohol. She then assays it for potency by two methods, complement fixation and direct inhibition of agglutinins, and administers it by intramuscular injection. According to Carter, Rh hapten appears to be a lipid substance which does not produce antibodies when injected into the experimental animal.

If a substance can really be prepared which can eliminate or reduce a sensitized person's Rh antibody titer this would obviously be of great value in the antenatal prevention of erythroblastosis. Carter has reported results of treatment with Rh hapten in a series of sensitized Rh-negative women, as well as a series of infants with erythroblastosis. Her report claims excellent results.

Again because of the importance of the subject, and the interest that Carter's report has aroused, preparation and assay of Rh hapten according to her technique and a study of its effects on patients were undertaken by me at the Blood Bank of the New York University-Bellevue Medical Center, formerly the New York Post-Graduate Medical School and Hospital. To be certain that there could be no question about the potency of the hapten used in these trials, most of the material used was either prepared by and furnished to me by Carter, or prepared at my laboratory and found satisfactory when assayed by her. Up to the present we ourselves have been unable to our satisfaction to confirm Carter's assay findings, although we have used the Kolmer complement fixation test and the direct inhibition of agglutinins as recommended by her. We have also tried the quantitative complement fixation method as applied by the New York State Department of Health for serologic diagnosis of syphilis. In some lots we have found evidence of fixation of complement but only in very low titer and of questionable specificity, even though when this same material was submitted to Carter's laboratory her report stated that it was potent and satisfactory. In most lots we have found no evidence of complement fixation. By the method of direct inhibition of agglutinins we have found little if any



effect. Here again we could not convince ourselves of its specificity; the reactions with anti-A and anti-B sera were similar to those with anti-Rh serum, suggesting that the effect was due to the alcohol or other nonspecific materials in the extract.

TABLE III. RESULTS OF TREATMENT WITH Rh HAPTEN

CASE 1 (PREGNANCY)			
NO.	INJECTIONS HAPTEN		Rh ANTIBODY TITER
	INTERVAL (DAYS)	DOSE (MG.)	
1	0	200	128
2	7	200	256
3	7	200	256
4	7	200	256
5	7	200	192
Result: Premature Rh-negative infant. Died within a few hours.			
CASE 2 (PREGNANCY)			
1	0	1M*	250
2	4	1M*	320
3	16	1M*	320
4	5	1M*	320
5	19	200*	320
-	3	-	320
Result: Normal Rh-negative infant. W. injections given and titrations done by Dr. A. S. Wiener.			
CASE 3 (NOT PREGNANT)			
1	0	1M*	24
2	14	1M*	8
3	14	1M*	12
4	14	1M*	12
5	14	1M*	8
6	7	100	8
7	7	200	8
8	7	200	8
9	1	200	-
10	1	200	4
11	1	200	-
12	1	200	8
13	3	200	4
14	3	200	8
15	1	200	4
16	3	-	8
CASE 4 (PREGNANCY)			
1	0	1M*	4
2	6	200	4
3	8	200	4
4	7	200	4
5	7	200	2
6	5	200	4
7	1	200	3
Result: Erythroblastotic infant. Replacement transfusion. Living and well.			
CASE 5 (PREGNANCY)			
1	0	200	6
2	7	200	16
3	7	200	16
4	7	200	32
5	7	200	24
6	1	200	-
7	1	200	-
8	2	200	32
Result: Erythroblastotic twins. Replacement transfusions. Living and well.			

In Table IV, a marked drop in IQ is seen for labors over 30 hours and under one hour. For all labors of 25 hours or under, multiparas have children with a lower IQ than primiparas, suggesting that the faster the labor the lower the IQ. Personality ratings are best (lowest) in the 25- to 30-hour group, and least favorable in labors over 30 hours, and second worse in the labors under one hour.

TABLE IV. HOURS OF LABOR

PERSON- ALITY RATING	IQ	PERSON- ALITY RATING	IQ	PERSON- ALITY RATING	IQ
<i>One Hour or Less</i>				<i>10 Multiparas</i>	
2.68	105.8			2.68	105.8
				5 males	99.8
				5 females	111.8
<i>Over 1, Through 5 Hours</i> 77 Cases		<i>9 Primiparas</i>		<i>68 Multiparas</i>	
2.36	109.86	2.1	114.22	2.39	109.25
Male	108.12	3 males	98.67	42 males	108.79
Female	112.66	6 females	122.	22 females	110.12
				Sex not mentioned in 4 cases	
<i>Over 5, Through 6 Hours</i> 93 Cases		<i>8 Primiparas</i>		<i>85 Multiparas</i>	
2.35	111.16	2.6	117.17	2.32	110.69
Male	110.3	4 males	125.5	43 males	109.02
Female	112.	4 females	113.	42 females	112.31
<i>Over 6, Through 15 Hours</i> 102 Cases		<i>44 Primiparas</i>		<i>58 Multiparas</i>	
2.55	110.37	2.6	112.14	2.5	109
Male	108.16	24 males	113.95	22 males	102.1
Female	112.	20 females	110.15	36 females	113.4
<i>Over 15, Through 25 Hours</i> 29 Cases		<i>19 Primiparas</i>		<i>10 Multiparas</i>	
2.37	111.58	2.2	111.94	2.71	110.75
Male	111.93	9 males	117.89	5 males	101.2
Female	111.17	10 females	106	5 females	126.67
<i>Over 25, Through 30 Hours</i> 4 Cases		<i>3 Primiparas</i>		<i>1 Multipara</i>	
2.05	110	2.2	109	1.6	112
<i>Over 30 Hours</i> 11 Cases		<i>4 Primiparas</i>		<i>7 Multiparas</i>	
2.75	102	2.25	99.75	3.18	103.28
Male	98.85				
Female	111.33				

Personality rating: 1, superior; 2, above average; 3, average.

Table V classifies IQ according to infant birth weight. Birth weights of 5 pounds or under are probably the best index of prematurity. (Only eight of this group were reported as premature; seven more were reported premature in the 5- through 6-pound group; and 17 babies over 6 pounds were considered premature by their mothers.) The results are a little surprising as the babies weighing 5 pounds or under have a higher IQ than the average for the whole series (111.9), while those over 5 through 6 pounds show a marked drop in IQ (105.24); however, the ones considered premature by their mothers in this group average 115. A significant drop is again seen when birth weights are over 9 pounds (108.8). Personality rates are best (lowest) in the 5-pound or under group and become steadily worse as the birth weights increase.

TABLE III—CONT'D

CASE 9 (NOT PREGNANT)			
INJECTIONS HAPTEN			Rh ANTIBODY TITER
NO.	INTERVAL (DAYS)	DOSE (MG.)	
1	0	200	64
2	6	200	64
3	7	200	64
4	7	200	96
5	7	200	96
6	4	200	64
7	3	200§	32
8	4	200§	48
9	3	200§	64
10	4	600§	64
11	3	600§	48
12	4	—	64
CASE 10 (NOT PREGNANT)			
1	0	200	32
2	7	200	32
3	7	200	64
4	4	200	48
5	5	200	32
6	2	200	64
7	4	200	48
8	3	200	64
9	4	200	48
10	3	200§	32
11	3	200§	64
12	4	400§	64
13	3	600§	48
14	4	600§	64
15	3	600	32
16	4		64
CASE 11 (NOT PREGNANT)			
1	0	1M*	64
2	7	200*	128
3	7	200*	64
4	7	200	64
5	7	200	64
6	7	200	64
7	4	200†	32
8	2	200†	64
9	4	200†	32
10	3	200	96
11	4	100†	64
12	3	200	128
13	4	400	32
14	3	200	64
15	4	400	96
16	30	500‡	64

M, 1,000 units.

\*Hapten prepared by and assayed by Mrs. Carter. A second source of hapten was that used for all injections without *any* symbol following the dosage in milligrams. This was prepared by our laboratory but assayed by Carter and declared satisfactory.

†Hapten obtained from a third source.

‡Hapten obtained from a fourth source.

§Material not assayed by Carter but prepared at our laboratory.

TABLE III—CONT'D

CASE 6 (NOT PREGNANT)			
INJECTIONS HAPTEN			Rh ANTIBODY TITER
NO.	INTERVAL (DAYS)	DOSE (MG.)	
1	0	200	48
2	5	200	48
3	5	200	96
4	7	200	32
5	7	200	48
6	7	200	64
7	7	200	96
8	7	400§	48
9	7	400§	64
10	7	200	64
11	7	400§	64
12	7	800§	32
13	7	600§	128
14	7	400§	128
15	7	400§	128
CASE 7 (INTERIM)			
1	0	200	512
2	5	200	256
3	7	200	256
4	7	200	256
5	8	200	256
6	6	200	384
7	7	200	256
8	7	200§	384
9	7	200§	512
10	7	400	384
11	7	400§	384
12	7	600§	384
13	7	600§	768
14	7	400§	—
15	7	400§	512
CASE 8 (PREGNANCY)			
1	0	200	16
2	7	200§	16
3	7	400	32
4	7	600	16
5	7	800	8
6	7	600§	32
7	7	400§	32
8	7	400§	16
9	7	400§	32
10	7	200§	32
11	7	200§	32
12	7	200§	32
13	7	200§	32
14	7	200§	32
15	7	200§	32
16	7	200§	32
17	7	200§	32
18	7	200§	24

Result: Macerated stillborn fetus. In this case and in Case 11 antibody titrations on identical specimens were carried out not only by our laboratory but also by that of Dr. Philip Levine with comparable results.

treatment make it advisable that it be used only under carefully controlled conditions until adequate statistical data are compiled. Vaccines should be prepared so that less frequent injections are necessary. Any therapy proposed for these patients should be tested critically and thoroughly evaluated, but with an open mind. In any event, during the developmental stage of any procedure one must be very conservative and be careful not to arouse false hopes in the minds of these unfortunate couples.

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De Voe, R. W., Lovelady, S. B., Dockerty, M. B., and Gray, H. K.: *Pregnancy Complicated by Presacral Neurofibroma, One of the So-called Middeldorpf Tumors; Report of a Case*, *Proc. Staff Meet., Mayo Clin.* 23: 239, 1948.

Tumors that obstruct the birth canal in pregnancy usually arise from the reproductive system, such as uterine fibromas and ovarian tumors, but in the case reported the tumor was extragenital. The patient in this case was twenty-four years of age when admitted to the Mayo Clinic. Eight months previously a pelvic tumor had been palpated at the time of a routine examination; at that time it caused no symptoms. Surgical exploration of the pelvis showed the tumor to be retroperitoneal and it was not removed. At the time of admission to the Clinic, a diagnosis of pregnancy of about three months was made. The uterus was retroverted and there was a firm mass anterior to the uterus that appeared to be fixed posteriorly to the sacrum. Operation was done for removal of the tumor without interruption of the pregnancy. On microscopic examination the tumor was found to be neurofibroma; no signs of other neurofibromas were found. This case is of interest to the obstetrician because incarceration of the uterus by the tumor or by adhesions might produce abortion; or, if the pregnancy went to term, the tumor would cause a serious impediment at the time of labor producing dystocia. Presacral tumors are rare, but routine physical examination and adequate prenatal care are necessary in case such a tumor complicates pregnancy, in order to prevent obstetric complications and needless operations.

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However, since the material is apparently harmless and since approved material was available, it was used for clinical trial. Table III gives a summary of the results of treatment with Rh hapten in eleven patients to whom a total of 130 injections were given. Fourteen injections were of hapten prepared and assayed by Carter. Five injections were of hapten obtained from two other sources. Seventy-three injections were of hapten prepared by us but assayed by Carter and declared satisfactory by her. Thirty-eight injections were of hapten prepared by us but not submitted to her for assay. Each patient received from five to eighteen injections. The time interval between most injections was seven days, although, as can be seen from Table III, this in certain instances was reduced to twice a week and even daily. The dose of most injections was 200 mg., but in some cases when no favorable effects were evident the dose was increased to 400, 600, and 800 mg.

In only one patient (Table III, Case 3) was there a decline in titer values, and this was slight in degree. In a second case (Table III, Case 5) there was a slight rise, while in the other nine cases there was no evidence of any ability on the part of Rh hapten, irrespective of the source, the dosage, or the frequency of administration, appreciably to change the titer of Rh antibodies in the blood of these sensitized women.

Six of the women treated were interim cases and five were pregnant. They all had typical marital histories. They all showed in their sera anti-Rh agglutinins, Rh<sub>0</sub> blocking antibodies, or both. They all had previously given birth to erythroblastotic children, stillborn children, or both. Of the five treated during pregnancy, one gave birth to a premature Rh-negative infant who died within a few hours. The second gave birth to a normal Rh-negative infant. The third was delivered of a macerated stillborn fetus. The fourth gave birth to an erythroblastotic infant, and the fifth gave birth to erythroblastotic twins. These three infants with erythroblastosis received exchange transfusions and are living and well.

### Summary and Conclusions

All of our attempts to date to reduce or eliminate Rh antibodies in the sera of Rh-negative women *already sensitized* to the Rh factor have been of little or no avail. Four women sensitized by the Rh factor were treated with exchange transfusions. However, in no case was there an appreciable change in the Rh antibody titer despite the use of enormous amounts of Rh-negative blood. Our results have also been negative when we used the so-called hapten as advocated by Carter. To test this material thoroughly 130 injections were given to eleven patients without appreciable effect. At the present time the only recourse open to luckless couples where the degree of Rh sensitization is extreme is to adopt a child or to resort to artificial insemination from an Rh-negative donor, or, if the husband is heterozygous, to take their chances that the next baby might prove to be Rh negative. In cases where the degree of sensitization is mild, it may be possible to save the baby by inducing labor prematurely and then by giving the infant, without delay, an exchange transfusion.

Obviously, the best results would be obtained if successful efforts could be made to *prevent Rh-negative women from becoming sensitized in the first place*. Eugenic marriages have been suggested but are impracticable. For the *prevention of sensitization* our results suggest that the proper application of countersensitization with harmless vaccines may possibly reduce the chances of Rh sensitization following the birth of an Rh-positive child. However, further experience with this procedure is necessary before a final conclusion can be drawn. Difficulties of proper "priming" and "timing" in applying such

glucose and bile, was negative for albumin, acetone, and diacetic acid. The blood pressure averaged 140/70 before the onset of true labor which began during the transfusion.

There was no external bleeding. The pulse rate rose to 170 per minute and the systolic blood pressure fell to about 80. Abdominal palpation revealed nothing to support a diagnosis of uterine rupture although the general picture was that of hemorrhage. Labor proceeded rapidly and a 6-pound stillborn fetus was delivered easily by the breech under cyclopropane-oxygen anesthesia. Plasma and whole blood were kept running into her veins while separation of the placenta was awaited. A moderate amount of vaginal bleeding was then noted. Since further blood loss was to be avoided, an attempt was made to remove the placenta manually. No line of cleavage was palpable and the exploring fingers went deeply into the myometrium. It was obvious that the placenta would not come free without tearing the uterine wall. The uterus was therefore tightly packed with gauze and the patient returned to bed. Her general condition was so poor that an attempt was made to improve it before hysterectomy was done. She was given repeated transfusions and oxygen by nasal catheter. She had a severe reaction to one transfusion so that three days elapsed before the laparotomy was performed.

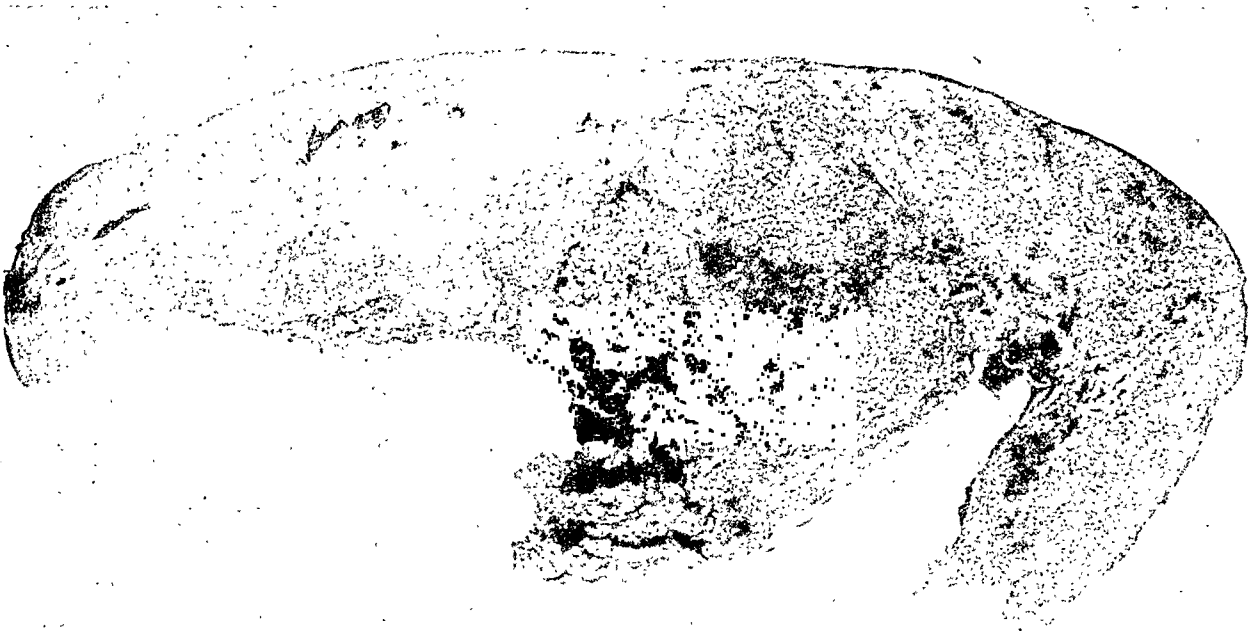


Fig. 1.—A sagittal section through the center of the placental site and the anterior uterine wall shows the rather abrupt transition between intact and invaded myometrium. The upper half of the anterior wall is replaced by intact chorionic villi. Diffuse subserosal hemorrhage is present in the region of the fundus. Thrombosis of many of the myometrial veins and the placental sinusoids is evident. A ragged necrotic membrane is attached to the endometrial surface below the placental attachment, in the region of the decidua vera. ( $\times 4/5$ .)

Under cyclopropane-oxygen anesthesia, the peritoneal cavity was entered and 1,500 c.c. of blood were removed by suction. An unmeasured amount of free blood was left in the peritoneal cavity. The uterus presented a most unusual picture; the right cornu and the top of the fundus were replaced by a spongy purplish mass. This mass was covered by serosa and many large dilated veins. The omentum was not attached to the fundus but had fragments of organizing blood clot attached to its lower margin. This indicated that the omentum had attempted to plug the bleeding area but had been torn loose during the severe uterine contractions incident to labor. The spongy mass had the appearance of placental tissue. The possibility of chorionepithelioma could not be disproved grossly. Cystic ovaries and a secondary mass in the left broad ligament supported this theory.

## PLACENTA ACCRETA COMPLICATED BY HEMOPERITONEUM

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PLACENTA accreta is defined as that pathologic condition in which the chorionic villi are in direct contact with and are interspersed among the actual muscle bundles of the myometrium. There is a deficiency of decidual tissue resulting in a partial or complete absence of this important structure. Attempts at separating such a placenta can lead only to tearing of the uterine wall itself, as there is no line of cleavage between the placenta and muscle.

The incidence of placenta accreta in different clinics varies widely from: The Boston Lying-in Hospital, 1 in 1,956 deliveries to 1 in 17,464 deliveries at the Baltimore City Hospitals. Irving and Hertig stress the fact that cases of partial placenta accreta are often overlooked and are spoken of as densely adherent placentas. The tissues removed should always be examined microscopically when any difficulty is encountered in manually removing a placenta.

There are at least 163 cases of placenta accreta reported in the literature to date, in which the diagnosis has been proved by microscopic examination. The case of placenta percreta reported below is remarkable in that it was complicated by massive hemoperitoneum in the absence of gross rupture of the uterine wall. The vaginal bleeding was minimal and the hemorrhage occurred into the peritoneal cavity from rupture of large subserosal veins.

The patient was a 24-year-old, white para 0, gravida ii. Her first pregnancy had ended in a spontaneous incomplete abortion at about six weeks with severe hemorrhage. She gave a history of having had a curettage, blood transfusion, and a febrile but eventually complete convalescence.

She became pregnant again six months after this septic illness. Her local physician treated her during the first five months for severe nausea and vomiting and irregular vaginal bleeding. She had no unusual complaints when seen by one of us (M. D. P.) six weeks before her calculated date of delivery. She appeared pale, undernourished, with very poor general hygiene, but her pulse rate, blood pressure, urinalysis, and abdominal examination were normal at that visit. Two weeks later she was admitted to the Albany Hospital with mild irregular uterine contractions. The abdomen was tender to the touch but she did not localize the tenderness. The cervix was a finger tip dilated and the fetal heart rate was recorded as 140 per minute. Her symptoms subsided promptly after a night's sleep and mild sedation. A second admission for apparent false labor with similar findings but intensified pain occurred one week after the first and she was again sent home. She returned twenty-four hours later appearing acutely ill.

On this third admission, the uterine contractions were intermittent and the fetal heart was definitely heard. No vaginal bleeding was seen. Very striking were the extreme and increasing pallor, the pinched expression of the face, and the rising pulse rate. The abdomen was tense, tympanitic in its upper half, but there was still no localization of tenderness or palpable abnormality of the uterus. The cervix was still a finger tip dilated.

A blood count revealed 1,780,000 red cells with 4.5 Gm. (31 per cent) of hemoglobin. Compatible blood was obtained and transfusion started. The urine showed a trace of



## Comment

In view of the varied etiology, it is probable that in each case of accreta more than one cause could be important. The instance described in this report can most reasonably be attributed to previous endometrial damage following postabortal sepsis. There was complete absence of decidual tissue at the placental site. Also in the areas away from the placental site, which should have showed decidua vera, cells of decidual origin were not identified.

## Conclusion

As far as could be ascertained from the literature, hemoperitoneum complicating placenta accreta in the absence of gross rupture of the uterus has not been described heretofore. The bleeding into the peritoneal cavity was caused by rupture of a large subserosal myometrial vein.

Whatever the cause of placenta accreta, it is safe to say that its presence constitutes a major obstetrical emergency. Abdominal hysterectomy is statistically the safest method of treatment, where hemorrhage is present, especially if attempts at manual extraction have been kept at a minimum.

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Brendemoen, O. J., and Brendemoen, C.: Anti-A and Anti-B Isoagglutinin Titers in Rh-Immunized Pregnant Women, *J. Lab. & Clin. Med.* 33: 1089, Sept., 1948.

The authors briefly review the literature concerning the problem of relationship between Rh and A or B immunization. They investigated 87 anti-Rh containing sera which were obtained among 25,000 samples drawn from patients in the last two months of pregnancy. As controls, 100 sera from Rh-negative nonimmunized pregnant women and 100 sera from Rh-positive pregnant women were used.

They obtained significantly lower anti-B titers in A and O blood of Rh-negative patients who had Rh antibody than in the control groups. The anti-A titers did not differ notably. A simple negative correlation between anti-B and anti-D titers could not be demonstrated. The general ABO and MN distribution was within normal limits. S. B. GUSBERG, M.D.

Salvin, Monte: Uterotubal Insufflation With Penicillin and Streptomycin Aerosols. A Preliminary Report, *West. J. Surg.*, page 500, Sept., 1948.

Nebulized penicillin and streptomycin for introducing the antibiotic directly to the site of infection was an outcome of techniques designed for the treatment of gas casualties in World War II. The idea has been employed for the treatment of pelvic inflammatory disease, utilizing the technique of uterotubal insufflation. A DeVilbiss nebulizer is attached to the insufflation apparatus and charged with 500,000 units of penicillin.

Prophylaxis against infection in the routine performance of the Rubin test has prompted the author to use the penicillin aerosol routinely in performing these tests. As a therapeutic procedure, the method requires further study, but the results thus far are encouraging.

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Therefore, the uterus, both Fallopian tubes and ovaries, and the broad ligament mass were removed. As soon as the bleeding was controlled, the patient's condition improved rapidly. Transfusion was given during the operation and postoperatively. Sulfathiazole powder was sprinkled liberally in the peritoneal cavity and later given by mouth. She had an amazingly calm convalescence and is well five years postoperatively.

*Surgical Specimen.*—A full-term postpartum uterus, with both ovaries and Fallopian tubes attached, showed a large, roughly circular zone of subserosal hemorrhage in the fundus with a jagged linear zone of erosion in the serosa. On section of the uterus, the upper one-third of the uterine wall was replaced by placental tissue (Fig. 1). The zone of transition between normal and invaded myometrium was sharp and distinct. The ovaries contained numerous follicular cysts and a large well-preserved corpus luteum of pregnancy.

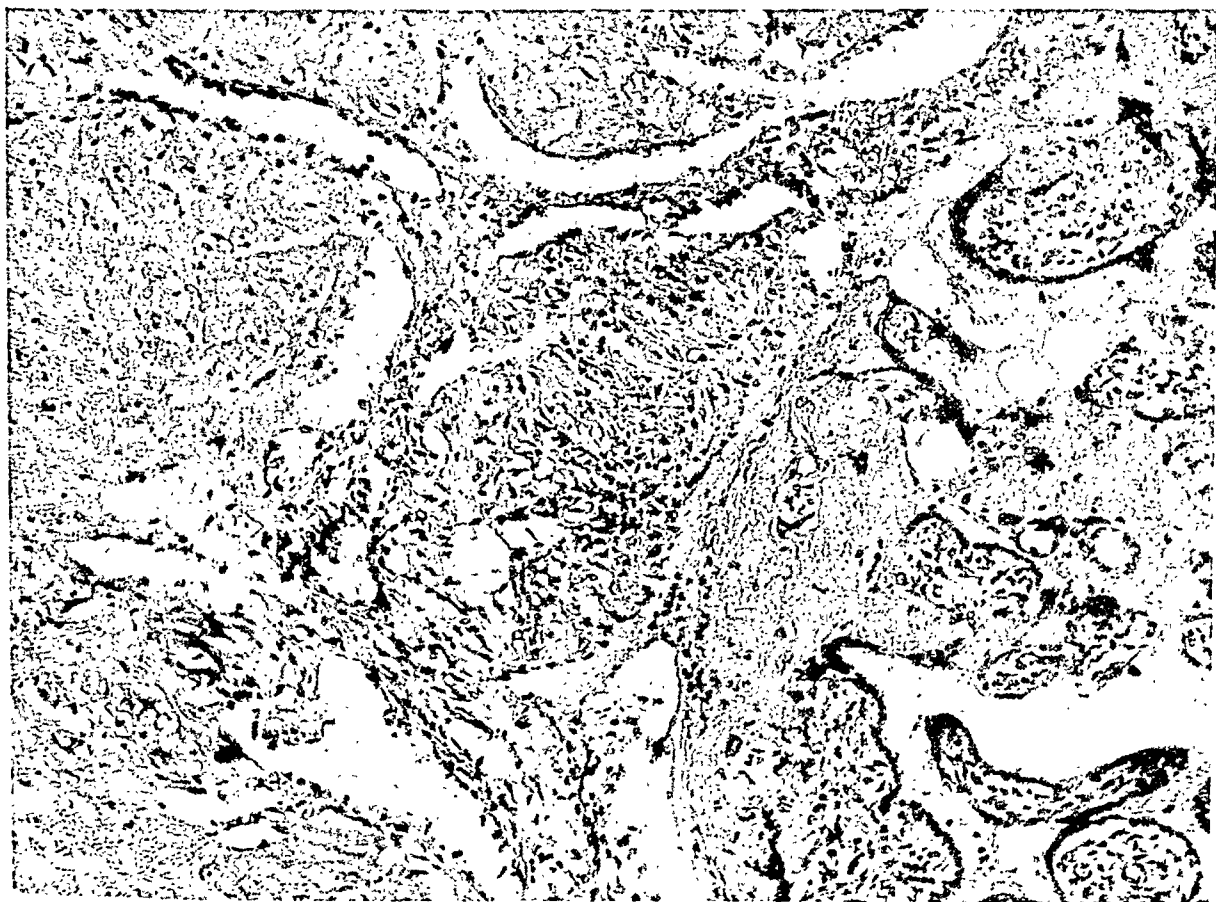


Fig. 2.—A high-power view is seen of the area of placental attachment. Chorionic villi and trophoblastic epithelial cells are in direct contact with partially necrotic and acutely inflamed myometrium, with no interposition of any decidual tissue. ( $\times 165$ .)

*Microscopic Description.*—A section through the anterior uterine wall revealed replacement of myometrium by chorionic villi. The villi, and in some situations isolated trophoblastic cells, lay directly on the myometrial cells (Fig. 2). Nowhere were any decidual elements seen. The fibrin stria of Nitabuch, usually associated with the decidua, was absent. The stria of Rohr was imperfectly formed and ill defined.

The left broad ligament mass proved to be composed of recent and organized blood clots. No tumor tissue was seen.

*Final Diagnosis.*—Placenta accreta with rupture of subserosal veins and hemoperitoneum; organizing and recent hematomata of the left broad ligament; follicular cysts of ovaries; corpus luteum of pregnancy.

Graham,<sup>5</sup> Foote,<sup>6</sup> Seibels,<sup>7</sup> and numerous other authors have reported the diagnosis of many early cancers by finding cells in the vaginal smear. Some of these have even been shown to be in a preinvasive or "carcinoma in situ" stage.

The Papanicolaou test offers its greatest contribution to the gynecologist in diagnosis and control of cervix cancer. Novak,<sup>8</sup> Te Linde,<sup>9</sup> Howard Taylor, Jr.,<sup>10</sup> and others have stated that squamous cancer has its origin in the squamocolumnar junction of the cervix. Walter Schiller,<sup>11</sup> who with the Schiller test has studied many early cervix cancers, goes so far as to state that 100 per cent of epidermoid carcinoma arises from the squamous margin of the squamocolumnar junction. If this is true, it means that cancer arises from a known spot no larger than a dime with greater frequency than from any other similar area in the human anatomy. Therefore, a method of sampling the squamous cells in this area periodically offers, first, a means of cancer control through early diagnosis while the lesion is still in a curable stage. Perhaps of equal significance is the fact that study of the cells in this region may throw further light upon the stage of cancer when it is in the process of becoming cancer.

One of the modifications of the Papanicolaou method is the "surface-biopsy" technique.<sup>12</sup> This may be defined as a scraping with a small wooden spatula of the squamous cells from the circumferential margin of this tissue at its junction with the gland epithelium of the cervix. The scraping gives a selective sample of cells removed prior to exfoliation. The cells are fresh and well preserved, and since their origin is known, a more definite interpretation may be made.

For the evaluation, clinical photographs are submitted of a number of examples of preclinical cancer of the cervix. These photographs of the cervixes indicate the absence of any clinical lesion recognizable or even suspicious of a carcinoma. These are examples of early squamous cancer of the cervix where the cancer is developing invisibly on the exposed vaginal portion of the cervix at the squamocolumnar junction. They are not hidden from view in the endocervix. In all of these cases the early cancers were detected by the surface-biopsy scraping and these photographs were taken in the operating room immediately before surgical biopsies were secured for confirmation of diagnoses. Some of the clinical data may be of interest to demonstrate the importance of the cervical scraping as a method of selecting the cervix which may require multiple or serial biopsy sections to arrive at the true tissue diagnosis.

CASE 1.—Mrs. B., aged 43 years, had no symptoms of carcinoma, although recent menstrual periods had been somewhat prolonged. The cervix showed a benign parous appearance with residual chronic cervicitis and visible Nabothian follicles. Vaginal smears on this case failed to demonstrate abnormal cells. It was apparent from the clinical picture that no ulceration had yet developed and that the squamous tissue appeared to be intact. At this early stage the accelerated exfoliation associated with friability and necrosis of cancer tissue has not yet developed. Scraping, however, with the cervical spatula removed organized clusters of cells whose morphological character gave the cytologist a clear-cut diagnosis of carcinoma of the squamous type. Subsequently, biopsies were secured from both the anterior and the posterior lips. Those from the anterior showed benign cervicitis. Those from the posterior revealed a small but infiltrating squamous carcinoma.

CASE 2.—Mrs. K., aged 32 years, complained of leucorrhea. Clinically, the cervix showed a moderately large circular erosion, a fairly common picture found in parous women. Undoubtedly, the routine treatment in this case prior to the days of the vaginal smear would have been to do an electrocauterization. There was nothing to incite suspicion to call for a biopsy, and further, if biopsies had been taken, it would have been a major problem to determine in which segment of the large squamocolumnar circumference (measuring 5 cm. in

## THE VAGINAL SMEAR. "PRECANCER" CELL STUDIES USING A MODIFIED TECHNIQUE\*

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IN MANY major advances in the history of medicine, the original discovery preceded practical use by several years. Fleming's discovery of penicillin, lay dormant in the research laboratories for ten years before its epoch-making significance became realized. The bactericidal properties of sulfanilamide were recognized by Heidelberger at the Rockefeller Institute as early as 1916. Similarly, for all we know, the cause and cure of cancer may be discovered ten years before our inadequate vision may register its true significance. One of the major advances of recent years in the cancer field followed this same pattern. It is now over twenty years since Papanicolaou<sup>1</sup> first reported finding cancer cells in human vaginal secretions. Only now are we beginning to utilize this most valuable diagnostic procedure for the saving of human lives.

The Papanicolaou techniques are having even more far-reaching applications to cancer diagnosis in the discovery by similar principles of cancer cells in the secretions of the lung, of the stomach, urinary tract, and other body secretions.

Since the beginning, there has been considerable skepticism and even antagonism to the vaginal-smear method. It has been asked, "What's wrong with the biopsy?". The surgical biopsy has been proved to be a reliable method of diagnosis. Even so, there has been no appreciable diminution in the death rate in uterine cancer in the last twenty years despite improvements in radiological and surgical techniques. Most gynecologists agree that the visualization of an early cervix cancer in clinical practice is an extreme rarity. Therefore, the early phase in the history of this disease is preclinical. The vaginal smear is adding an abundance of evidence to prove this concept. Papanicolaou,<sup>2</sup> Meigs,<sup>3</sup> Jones, Neustaedter, Mackenzie<sup>4</sup> and others have reported cancer cells found in vaginal secretions in women whose cervixes exhibit clinical benignancy. In the past, biopsies have only been taken on cervixes which exhibit a suspicion of malignancy. Unfortunately, it is still true that most gynecologists do vaginal smears only on cases where the cervix bleeds or looks suspicious. Most of them have not yet reached the stage of ordering them on the normal-appearing cervix; yet from this group come the most dramatic finds.

\*Presented at the New York Academy of Medicine, Section on Obstetrics and Gynecology, Oct. 27, 1948.

TABLE V. WEIGHT OF BABY

PERSON- ALITY RATING IQ			PERSON- ALITY RATING IQ			PERSON- ALITY RATING IQ		
<i>5 Pounds or Under, 13 Cases</i>			<i>4 Primiparas</i>			<i>9 Multiparas</i>		
	2.22	111.9		2.9	101.		2.12	116.78
4 males	2.33	116	2 males	2.45	108.5	2 males	2.2	123.5
9 females	2.18	110.11	2 females	2.45	93.5	7 females	2.1	114.86
<i>Over 5 Pounds, Including 6 Pounds, 22 Cases</i>			<i>9 Primiparas</i>			<i>13 Multiparas</i>		
	2.4	105.24		2.01	108.3		2.36	102.9
14 males	2.49	106.7	5 males	2.6	108.	9 males	2.42	104.9
8 females	2.21	103.9	4 females	2.2	108.75	4 females	2.22	99
<i>7 Cases of 5 to 6 Pounds Group Listed as Premature</i>			<i>6 Primiparas</i>			<i>1 Multipara</i>		
	2.34	115.43		2.4	117		2	104
4 males	2.68	116.5	4 males	2.68	116.5			
3 females	1.9	114	2 females	1.85	119	1 female	2	104
<i>Over 6, Including 7 Pounds</i>			<i>22 Primiparas</i>			<i>48 Multiparas</i>		
	2.31	109.85			111.4			109.6
70 cases		107.07	9 males		115.1	22 males		103.33
31 males		112.05	13 females		108	26 females		114.09
39 females			<i>53 Primiparas</i>			<i>127 Multiparas</i>		
<i>Over 7, Including 9 Pounds</i>				2.52	113.1		2.43	109.47
180 cases	2.45	110.48	33 males		112	65 males		107.91
98 males		109.29	20 females		114.93	62 females		110.95
82 females		111.92	<i>24 Primiparas</i>			<i>33 Multiparas</i>		
<i>Over 9 Pounds, 60 Cases</i>				2.6	111.88		2.59	106.79
	2.59	108.8	16 males		112.31	19 males		103.05
36 males		106.73	8 females		111	14 females		111.86
24 females		111.88						

In Table VI, intelligence quotients are classified according to maternal weight gain. The best IQ is in infants whose mothers gained 18 to 25 pounds (115.1); and a steady decrease is seen as the pregnancy gains increase (105.3 for gains over 35 pounds; 98.2 for multiparas). Personality ratings have the same trend, being best if the maternal weight gain was 18 pounds or under and worst if the increase was 30 to 35 pounds.

TABLE VI. MATERNAL WEIGHT GAIN

PERSON- ALITY RATING IQ			PERSON- ALITY RATING IQ			PERSON- ALITY RATING IQ		
<i>18 Pounds or Under, 72 Cases</i>			<i>22 Primiparas</i>			<i>50 Multiparas</i>		
	2.33	109.34		2.44	109.48		2.29	109.28
		7.51			7.13			7.68
<i>Over 18 Pounds, Through 25 pounds, 68 Cases</i>			<i>31 Primiparas</i>			<i>37 Multiparas</i>		
	2.34	115.1		2.35	115.2		2.34	115.01
		7.82			7.72			7.89
<i>Over 25 Pounds, Through 30 Pounds, 27 Cases</i>			<i>8 Primiparas</i>			<i>19 Multiparas</i>		
	2.48	108.75		2.06	112.57		2.64	107.34
		8.23			8.16			8.26
<i>Over 30 Pounds, Through 35 Pounds, 5 Cases</i>			<i>2 Primiparas</i>			<i>3 Multiparas</i>		
	3.3	107.2		2.95	101.5		3.5	111
		7.61			6.13			8.6
<i>Over 35 Pounds, 14 Cases</i>			<i>8 Primiparas</i>			<i>6 Multiparas</i>		
	2.72	105.3		2.87	109.7		2.53	98.2
		8.52			8.28			8.83

diameter) to obtain biopsies. The value of the scraping technique is well demonstrated in this type of case. A single circumferential scraping from the squamous margin revealed great clusters of cancer cells and of cornified cells, giving a clear-cut cytological picture of squamous cancer. It is a significant point frequently observed by us in securing scrapings from the preclinical cancers, that in this early preulcerative stage the scraping does not usually injure the malignant zone sufficiently to induce bleeding from the site, in marked contrast to the well-known behavior when a friable clinical cancer is traumatized. This case demonstrated the need for most careful and adequate sectioning of tissues to obtain pathological confirmation. After seventy-nine sections had been cut from four segments of the squamocolumnar junction, the diagnosis of carcinoma was not yet established. Only after an additional thirty sections were cut was the nest of squamous carcinoma found.

How early in the history of cancer may a diagnosis be made? Is there such a thing as a "precancer" or cancer precursor stage? Is the transformation of the cell from a benign to a malignant state a gradual or rapid transformation?

Much of the basic knowledge of cancer learned to date has been acquired through the study of the pathology of tissues obtained by biopsies, but biopsies were usually excised only in the presence of advanced and clinical disease. Recent studies suggest that by focusing the light of existing knowledge upon the individual cell, more may be learned concerning the change in that cell from a benign to a malignant type. Studies of cells scraped from the cervix under all possible environmental conditions, i.e., in good health, under conditions of acute, subacute, and chronic inflammation, in the presence of erosions, or leukoplakia, or ulcerations, promise to open a new world of understanding of cellular response to gynecological disease processes.

It has been stated by Traut<sup>13</sup> that the vaginal smear represented the most important single diagnostic test in the armamentarium of the gynecologist. We are in hearty agreement with him, and, indeed, feel too that to the student of cancer the opportunity for study of the inflammatory, hormonal, and other environmental changes which may influence the cell may best be afforded by the utilization in the hands of the experienced cytologist of the surface-biopsy modification of the Papanicolaou technique.

After studying many thousand samples of cells from the cervix in normal cases, in inflammatory lesions and malignant lesions, it has been found possible to make an attempt to sort out the different cell types on the basis of the nuclear and cytoplasmic morphology of the cell stained by the brilliant Papanicolaou stains and other more recently developed staining methods.

Four types of cells may be recognized. By far the great majority of cells sampled in this region exhibit the morphology of normal benign cells. Another group of cases may be placed in the category of inflammatory hyperplasia. Then a third group exhibits the morphology of malignant cells as described by Papanicolaou. We may often diagnose a cancer as a preinvasive lesion by the appearance of the cells in the scraping. The surface-biopsy scraping, however, has revealed what we visualize to be a fourth type of cell midway between the inflammatory and the malignant and exhibiting certain similarities to both. While the changes in these cells are not sufficiently marked to indicate to the cytologist that they are cancer cells, he nevertheless is impressed with the conviction that if they are not a malignant type of cells, they are the next thing to it. Similarly, a pathologist studying a doubtful biopsy from the squamocolumnar region may see a picture which he feels to be very close to a cancer, yet there is insufficient evidence to enable him to call it cancer. Frequently, in such cases, if more sections are cut a small cancer will be found. In others, even with serial sections, no cancer is found and the most extreme pathological

picture remains that of a borderline lesion. This is the case type under discussion today. Is there a transition phase, a real "stepping-stone," as Novak has described, "between the benign and the malignant"? The great James Ewing has stated, "It is not true that a pathological condition must be either cancer or not cancer. It may be neither one nor the other. It may be in the process of becoming cancer." The surface-biopsy scraping gives a very sensitive evaluation of a trend to cancer morphology in squamous cells developing in the circumferential margin of the cervix. Are we justified in calling these transitional cell types "precancer" cells? Is there such a thing as a "precancer" cell? We do not presuppose to be able to answer this question or to prove that the cells shown are precancer cells, but certain evidence will be presented which tends to suggest that we are studying a type of cell which is related to the formative stage of cancer. Those who have studied only with the use of the simple aspiration from the vaginal pool may not find familiarity with this cell type except as an occasional atypical cell finding. Our studies have indicated that accelerated exfoliation is not the rule at this stage and adequate concentrations of these cells may best be obtained by a surface-biopsy scraping technique. Only by having an adequate collection of these cells in the microscopic field is it possible to attempt any interpretation of such cells.

May I emphasize again that the majority of precancer cell findings have been detected in cervixes exhibiting a benign appearance. Therefore, in the past, biopsies have been taken most infrequently, but the surface scraping has revealed concentrated collections of these cells, which have impressed us with their character as being a transitional type of cell on the border line between an inflammatory and cancerous change. These squamous cells have been described by us as the "precancer cell complex." The following morphological features have been observed to constitute this complex:

1. A persisting high concentration of cornified cells in the cervical scraping. The cytological picture is that of a continuous estrogenic or regenerative phase, the cornification level corresponding with the usual maximal level found at mid-cycle (preovulatory).
2. Atypical or "precocious"\* cornified cells (Figs. 3, 4, 5).
3. Cell giantism (Fig. 1).
4. Abnormally large hyperactive and immature nuclei with hyperchromatic staining, and frequent cytoplasmic granules (Fig. 5).
5. Multilobulation and multinucleation in nuclei of all strata of the squamous layer, deep (Fig. 7), middle and superficial (Fig. 2).
6. Hyperplastic basal cells (Fig. 7).
7. Perinuclear "halo" frequently noted in superficial cell types (Fig. 6). This halo has been observed commonly at the expected time of ovulation. Possibly some hormonal alteration with the cell at this stage of development may account for this morphological phenomenon found in inflammatory as well as in early malignancy cases.

Many of these cells show evidence of a degree of immaturity. The surface cells show "precocious" cornification and accentuated keratinization. Comparative studies on the cornification process of squamous cells of the oral cavity compared to those of the vagina indicate certain similarities in the precancer cells of the cervix to those observed in oral leucoplakia. W. Burton Ayre, who has been conducting these comparative studies, states that in leucoplakia of the tongue, the disorder seems to have important systemic etiological factors and, due to the lack of some nutritional or hormonal factors, the intrinsic cell dy-

\*A term originated by Dr. Robert Chambers.

namics concerned with the maturation and cornification process do not operate in the usual manner, and cornification and keratinization of the cell occur at an earlier than usual stage. Certainly, in the cervix many of the superficial cells show indications of disorder in the cornification process in cancer and in precancer. Certain environmental factors may be determined concerning the cells involved in this stage of cancer. There is usually some evidence of chronic

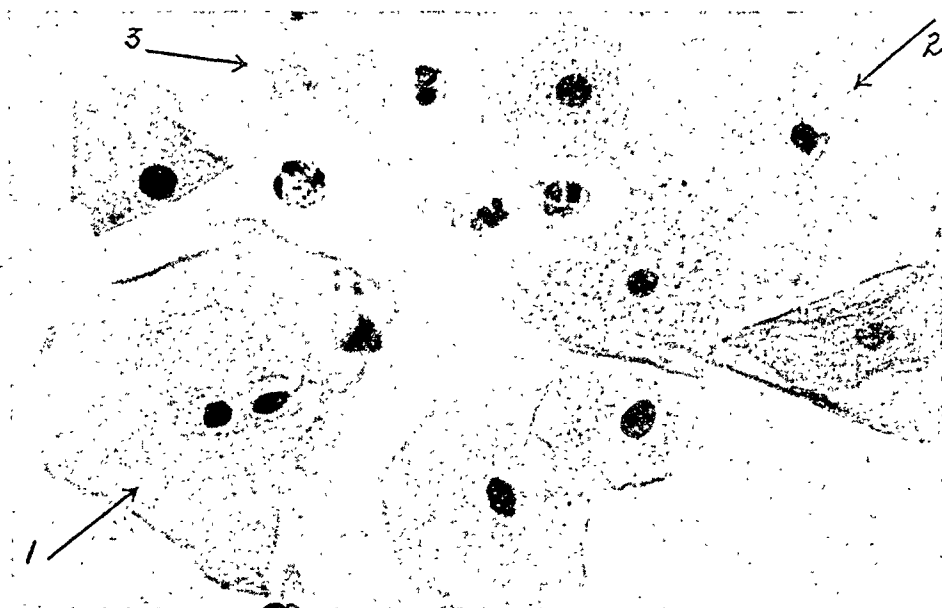


Fig. 1.—Precancer cell complex. Group of superficial cornified cells with atypical features. Large cell (No. 2) is a typical example of a normal, mature, cornified cell. All cells in group, except No. 3, show acidophylic staining. No. 3 is basophilic and shows lighter staining. Observe giant double-nucleated cell (No. 1.).

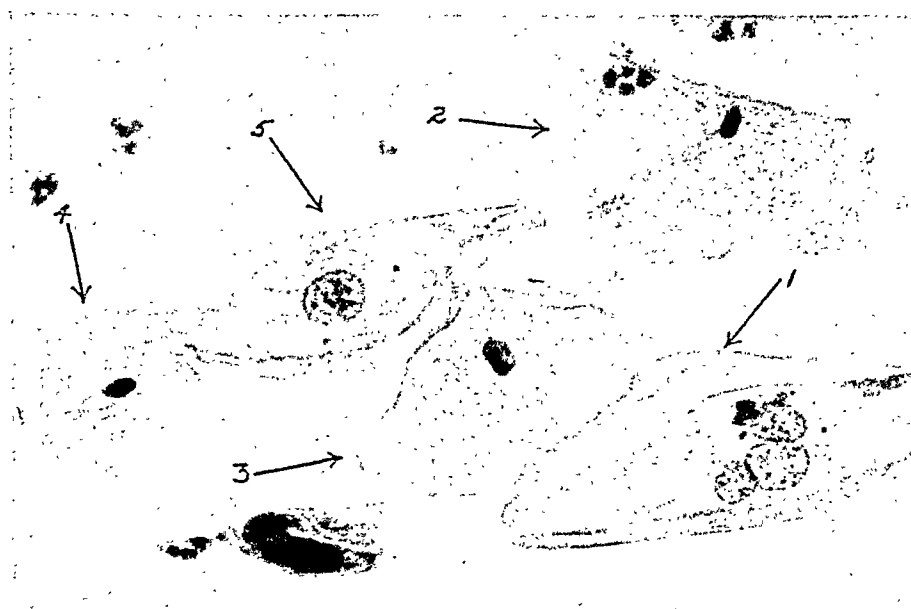


Fig. 2.—Precancer cell complex. Superficial cells showing atypical cornification. Observe multinucleation in cell No. 1. All cells show acidophylic (cornified) staining. Cells 2, 3, and 4 appear normal, while cell No. 5 has an abnormally large nucleus.



cervicitis involving the glands of the endocervix (Neisser). There is a concentration of cornified cells in the region of the squamous margin. There is a limited amount of evidence to suggest deficient excretion in these patients of thiamine and riboflavin, which may be linked with the finding of persisting high cornification (an index of impaired estrogen metabolism).

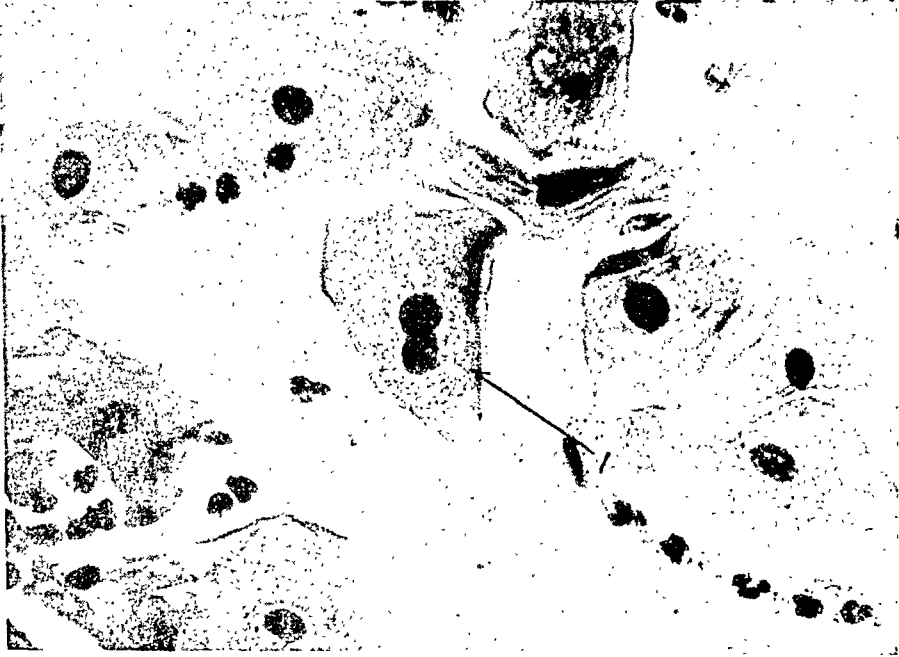


Fig. 3.—Precancer cell complex. Atypical cornification. Observe dumbbell-shaped nucleus (No. 1) and abnormally large hyperchromatic nuclei in most of the surface cells.

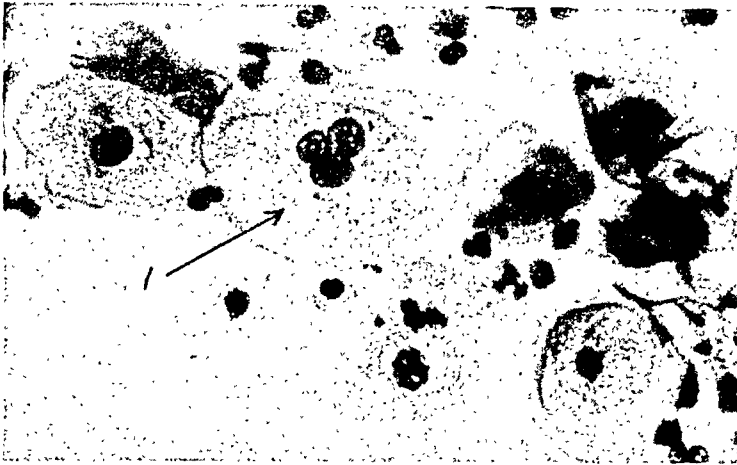


Fig. 4.—Precancer cell complex. Observe tri-lobate nucleus in surface cell which shows acidophylic staining reaction. Such cells have been termed "precocious cornified cells," a characteristic of the precancer state.

Brief mention should be made here of the clinical and cytological findings in various acute and subacute inflammatory states of the vaginal tract. These studies would tend to favor some etiological relationship between inflammation and cervical cancer. In the acute and subacute stages of trichomonad infestation

or a specific Neisserian infection, the purulent or mucopurulent secretions contain squamous cells exfoliated in great profusion from the exudative tissues. As the infection undergoes resolution, the vaginitis clears and finally the cervix resolves with a diminution or disappearance of the purulent secretion coinciding with clinical resolution. The endocervical glands are the last part of the vaginal tract to undergo resolution, and a chronic focus of infection remains in the vulnerable racemose glands centering around the squamocolumnar region. During

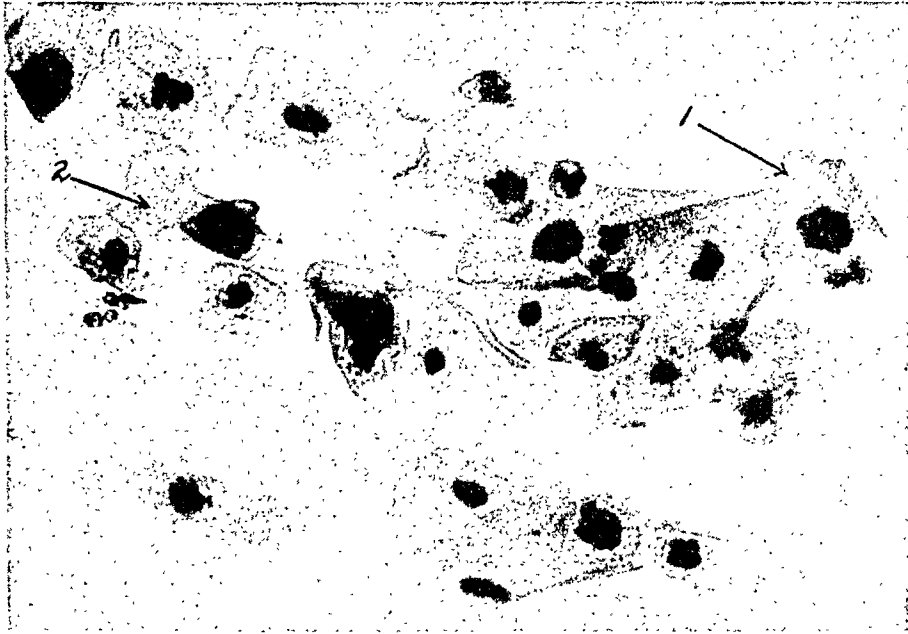


Fig. 5.—Precancer cell complex. Group of surface cells showing nuclear irregularities and hyperchromatic staining features characteristic of the precancer cell complex. All of the cells in this group show acidophylic staining of the cytoplasm. Note the large irregular hypertrophic nuclei in cells of types No. 1 and No. 2, examples of precocious cornification.

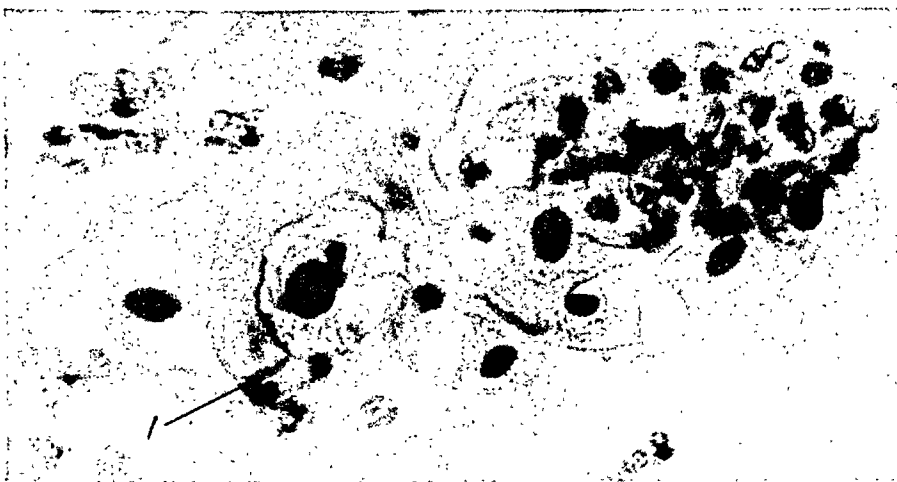


Fig. 6.—Precancer cell complex. Perinuclear halo well marked in several cells of this group. Note also large size and deep staining of the nuclei.

the acute phase, studies of the cells in the purulent vaginal secretion show nuclear and cytoplasmic changes, the nuclei showing an indistinct diffuse staining reaction with generalized enlargement of nuclei. Some degree of nuclear multilobulation may be noted. The cytoplasm shows a tendency to a diffuse indistinct

acidophilia simulating cornification but referred to as pseudo-cornification. It will be seen that these cells seem to represent a steppingstone between normal cells and the cell described as a "precancer cell." A neophyte in cytological interpretation may readily confuse these inflammatory cells with precancer or even with cancer cells. There are definite differences, however, which tend to suggest that the precancer state is something more than an inflammatory state. Although prolonged chronicity may be one of these factors, undoubtedly something else would appear to be added before a definite precancer or cancer status may develop. The frequency of precancer cell findings is roughly similar to that of cancer.

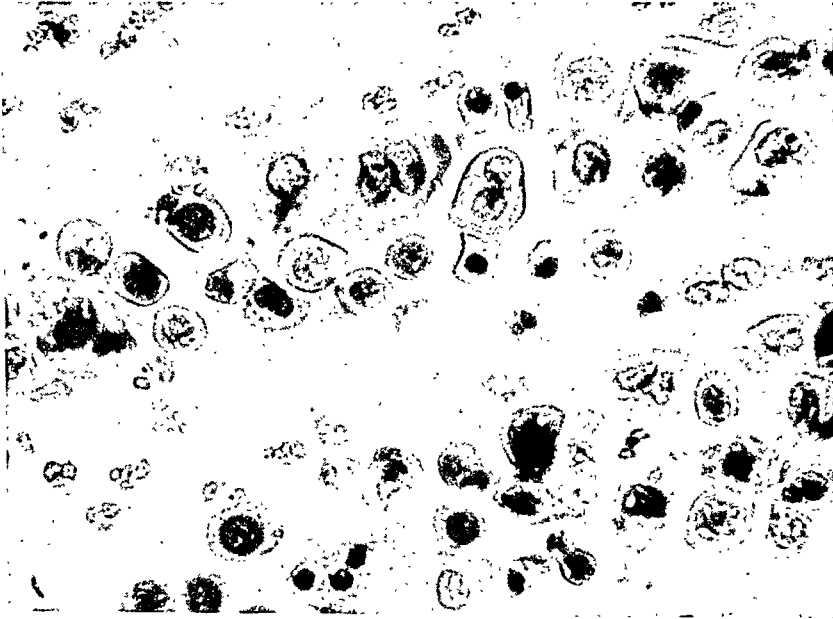


Fig. 7.—Precancer cell complex. Hyperplastic basal cells. Observe numerous binucleated cells and multinucleated nuclei.

Clinically, most of the precancer cases show no visible evidence of inflammation or of growth. Some show a minimal chronic cervicitis or an erosion, but these are common findings with cells of normal nuclear character. Vaginal smears on many precancer cases are negative except for an occasional atypical nucleated form. Cervical scrapings from the squamocolumnar junction, however, reveal concentrations of cells with the following features not shared by inflammatory cells.

1. The nuclei exhibit a greater deviation from normal with exaggerated multilobulation.
2. The staining shows a clear-cut definite picture in both the cytoplasm and the nucleus.
3. The nuclei show hyperchromatic staining approaching that of cancer cells. Selective staining achieved by the Papanicolaou stains appears to be an important diagnostic feature.
4. These precancer cells arise only from this one area, the marginal circle of squamous tissue, and marked exudation is usually not present.
5. Immediately adjacent to the precancer zone, concentrations of mature morphologically normal cornified cells are found, though in some cases there is found an admixture of pseudo-cornified (inflammatory) cells.

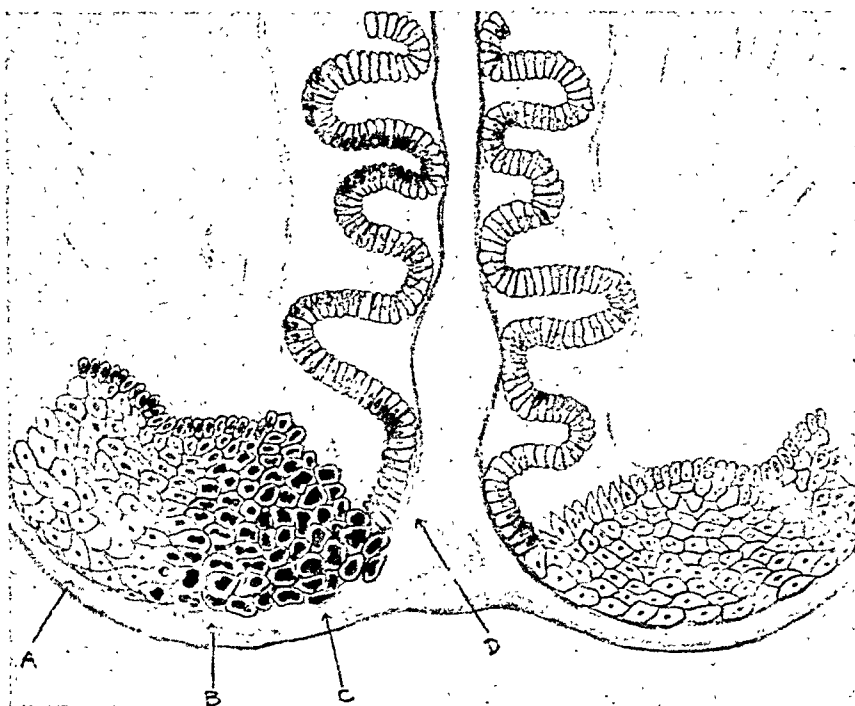


Fig. 8.—Diagrammatic representation of architecture of cervix. Observe squamocolumnar junction, the site where squamous carcinoma originates. Note normal squamous cells (A), borderline or precancer cell types (B), and cells of malignant morphology (C). D represents the cylindrical endocervical epithelium. While in the fixed surgical specimen the squamocolumnar junction assumes an endocervical position, in the physician's office eversion with a bivalve speculum causes the junction to assume an ectocervical position where the vulnerable cells are readily accessible to the cervical scraping.

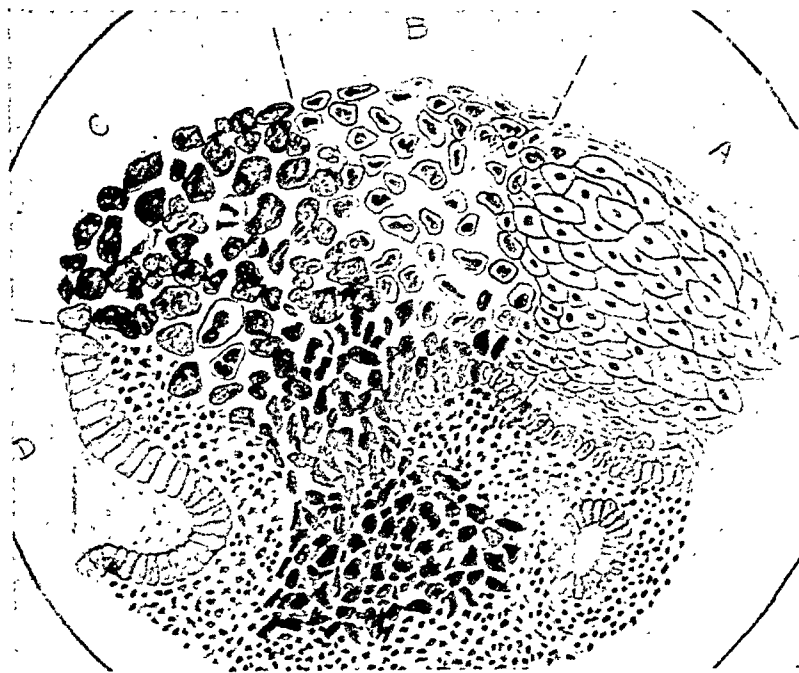


Fig. 9.—Diagrammatic representation of a high-power view of squamocolumnar region in early carcinoma. The cancer zone is represented by (C). Note anaplasia, hyperchromatism and early evidence of invasiveness. Immediately adjacent to the cancer zone is the precancer zone (B), where cells of the precancer complex type are found. Normal squamous cells, with cornified elements along the surface, are found in zone (A). D represents zone of glandular epithelium of endocervix.

It is important that a differentiation be made between a routine vaginal smear and a cervical scraping. Accurate precancer diagnosis is dependent upon the surface-scraping technique as the dilute vaginal pool is unreliable for the demonstration of precancer cells.

In the early preclinical microscopic stage of cervix cancer a concentration of normal cornified cells is found peripheral to the cancer. Approaching the cancer, cells with precocious cornification are noted. These are of the precancer type. Then the cancer cells themselves are still more immature, and usually exhibit complete failure of the cornification process.

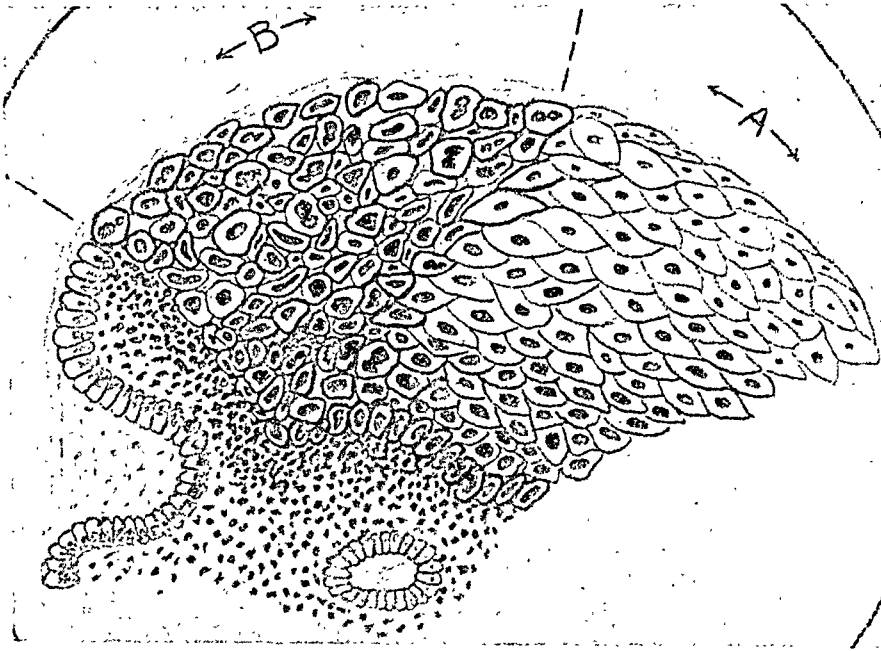


Fig. 10.—Diagrammatic representation of squamocolumnar region in true precancer cell complex case. The surface-biopsy scraping in these cases fails to show cancer cells, but shows clusters of the cells of precancer type and many cornified elements from the adjacent normal epithelium (A).

How are we going to evaluate these cells? The first procedure is to do adequate biopsy studies. These have usually revealed an interesting and puzzling picture in which hyperplasia and a degree of anaplasia are evident with the same atypical nuclei found extending from the base up to the surface. These lesions have been variously diagnosed as secondary squamous hyperplasia, precancer, hyperkeratosis, anaplasia, and some border into the entity called intra-epithelial carcinoma or carcinoma in situ. Prophylactic therapy in most cases demands conservative removal. Such cases, once the lesion is removed, may no longer be studied. Premature or radical surgery is hardly justified and surely the importance of the problem warrants careful clinical and cytological observation.

The next procedure in the evaluation of this cell complex is to study their behavior. The surface-biopsy technique enables us first to detect these cases and then to study their subsequent progress. Do these lesions regress and the precancer cells disappear spontaneously, or do they persist and become progressive, developing into carcinoma? At the present preliminary stage of our knowledge, investigation of behavior has been inadequate to provide any degree of certainty. However, some contributory observations have been made in individual cases which were followed closely. It has been asked, "Is this a normal

healing proliferative cell?" Healing erosions don't show them, even after cauterization.

First, let us consider reversibility. While many cases exhibiting inflammatory hyperplasia have been observed over a period of months to regress and disappear, this spontaneous regression has not been observed in the precancer complex cases. Some of these have been followed without surgery for one to three years. In these, the precancer cell type has persisted, while in five untreated patients progression to carcinoma (verified by tissue study) has been noted. Several of these will be discussed briefly.

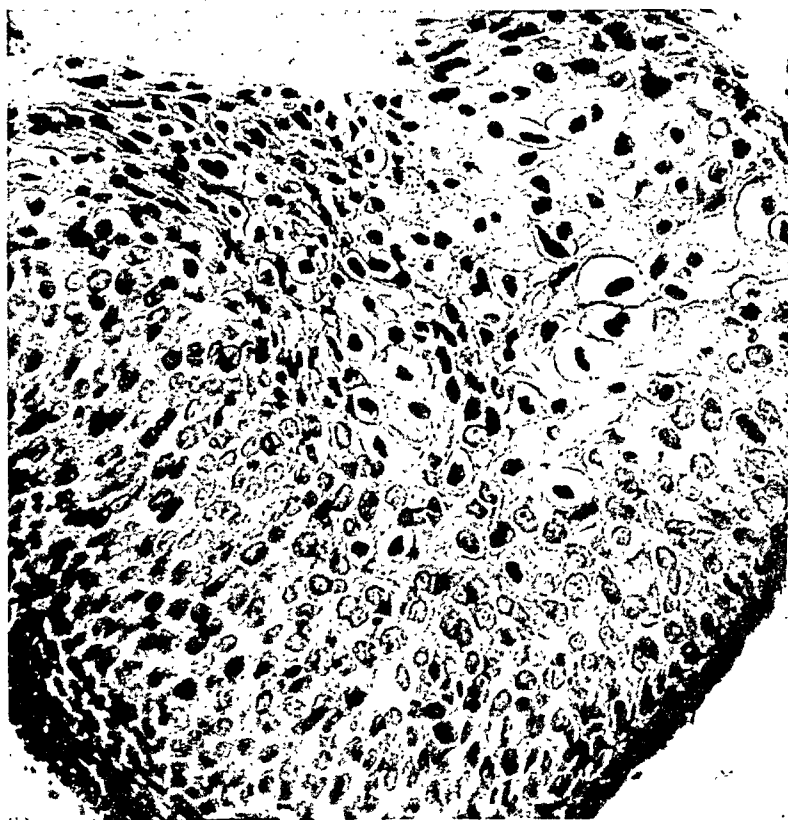


Fig. 11.—Cervical biopsy from squamocolumnar region in the type of case represented in Fig. 10. Observe many atypical and multiobulated nuclear forms throughout this tissue; yet serial sections failed to show evidence of genuine carcinoma. This tissue shows the origin of the atypical precancer cells found in the cervical scrapings.

**PRECANCER CASE 1.**—One of the cases studied was that of a sister of one of our technicians, a nulliparous woman, aged 29 years, complaining of irregular menstrual bleeding. The cervix appeared normal. Vaginal smears revealed a persisting high cornification of the regenerative phase peak without evidence of ovulation. Cervical scrapings revealed cells of the precancer complex. Clinically, this patient showed no progression over the course of a full year. The lesion was not treated locally or removed by surgical biopsy. Cytologically, the cells became more active in appearance. A ring biopsy of the squamocolumnar circle was performed with the cone-knife<sup>14</sup> and following serial sections a lesion diagnosed as intramucosal carcinoma at the squamocolumnar junction was found. At this stage its rate of growth would appear to be slow. Only two mitotic figures were detectable in serial sections of the entire noninvasive growth. This patient had no further treatment than complete excision with the cervical cone-knife followed by electro-conization and subsequent vitamin B therapy. For a year following the operation, the patient showed normal cervical scrapings. She is now pregnant and continues to show normal cytology. Of course, she will be kept under close observation, having careful cytological examinations for some years.

While evidence reported by Te Linde, Pund, Taylor, and others indicates slow progression in many preinvasive cervix carcinomas to an invasive and clinical stage over a period of several years, there is evidence too that different cancers may and do progress all too rapidly.

PRECANCER CASE 2.—Mrs. L, 40 years of age was curetted for bleeding in December, 1947. Her first cytology test was diagnosed four months later as "precancer." Two months later it was still reported as "precancer." She was kept under observation and developed intermenstrual bleeding which prompted a return to her gynecologist and this time, four months later and nine months since the first test, a third cytology scraping was taken. The cytological diagnosis was positive for cancer cells, and a ring biopsy with serial sections was required to reveal this cancer as an early invasive lesion. While, undoubtedly, some lesions may persist in a precancer and in a preinvasive cancer stage for many months or years, this lesion was already launched on its invasive career, and presumably soon would have become a clinical ulcerating malignant growth.

PRECANCER CASE 3.—Mrs. L, aged 28 years, was picked up in routine screening in Clinic. An initial diagnosis was made of "precancer" cells. Subsequent follow-up four months later showed cells of cancer type in her surface-biopsy smears. While pathological opinions vary on the lesion, most call it either preinvasive cancer or early invasive cancer. The lesion showed marked mitotic activity suggestive of rapid progression.

PRECANCER CASE 4.—Mrs. W, aged 42 years, with a diagnosis of precancer, was studied at three-month intervals with an unchanging picture for eighteen months. Finally she began to have menorrhagia and some irregular bleeding. Although the resident took a single biopsy on this case, the tissue studied was negative and radium was inserted. The patient is still being followed. We feel that adequate biopsy study would have revealed the origin of the abnormal cells. This case perhaps contributes little except that the patient showed persistence of the abnormal cells.

PRECANCER CASE 5.—The case of Mrs. J, 39 years of age, was diagnosed by cell smears mailed from Montana. The first cell scraping was diagnosed as precancer. Six months later a repeat cytology was diagnosed cancer. Biopsy with serial sections was advised. Dr. Hawkins of Helena, Montana, could see no cancer, but did a circular amputation of the cervix, and sent the entire specimen to us to do serial sections. The tissue showed early invasive cancer.

PRECANCER CASE 6.—Mrs. B., aged 48 years, had an initial diagnosis of precancer cell complex and six months later of carcinoma. The patient was admitted to hospital and the resident took a single surgical biopsy which proved to be negative. Although this patient has not since returned to our clinic, attempts are being made to secure additional cytological and tissue studies.

PRECANCER CASE 7.—The case of Mrs. P, aged 36 years, was detected by routine surface-biopsy and diagnosed as precancer. Three months later a repeat scraping was diagnosed again as precancer. Three months later a repeat scraping showed cancer cells (six months after the first test). Multiple biopsies were needed to locate lesion diagnosed as early invasive cancer by our pathologists. At this early stage, this cancer did not exhibit friability and bleeding when scraped with the spatula.

Experimental therapy to patients showing precancer cells has to date yielded certain information, mostly of a negative type. For example, certain cases were studied to determine whether large doses of vitamin B complex may cause disappearance of the cells in the smear. This has not been found to be true. Similarly, diophterin, terophterin, penicillin, sulfanilamide, testosterone, and progesterone have all been tried with negative results. Very promising preliminary results have been obtained by combining massive doses of the

It is of interest that the infant birth weights increase in all groups as the maternal gain increases (except the five cases listed under 30- through 35-pound gain and in this group one 4-pound premature infant distorts the average).

NO. OF CASES	GAIN IN POUNDS	NO. TOXIC	PER CENT TOXIC
72	18 or under	5	6.94
68	18 to 25	8	11.77
27	25 to 30	3	11.11
5	30 to 35	3	60.0
14	Over 35	1	7.14
Per cent toxic of entire series			10.38

Sex is another factor affecting IQ. In all the tables, the females have a higher IQ than the males except the 13 jaundice, 13 premature, and 6 eclamptic cases. (For the entire series, male IQ is 108.2 and female IQ is 112.12.) Unless the hereditary trait for the mentality is sex linked, the IQ should be equal. Possibly the differences in IQ could be explained by an increased vulnerability carried in the sex-determining chromosome for males. This is partly substantiated by the amount of difference in IQ for different types of delivery:

- Spontaneous: Male IQ 3.42 points lower than female IQ
- Forceps delivery: Male IQ 5.39 points lower than female IQ
- Breech delivery: Male IQ 7.64 points lower than female IQ
- Cesarean section: Male IQ 5.8 points lower than female IQ (5 of the 7 sections were performed upon toxic patients)

In larger series, the jaundice seen with Rh sensitivity is more disastrous to the male as far as death rate goes. The 13 jaundice cases in this study were born before Rh testing was done, and are too few to be significant.

Personality ratings for males show the opposite (by a narrow margin of 0.02 points). Since personality ratings include initiative, leadership, and industriousness, perhaps it is not surprising to find the males averaging higher here than in the IQ rating.

Skill of the obstetrician is another factor, as the average IQ of the children delivered by the one doctor having special obstetrical training was 113.06. The series average was 110.04. Personality rating was 2.39 in his group, less favorable than the 2.27 for the entire series.

In Table VII, a comparison of parity is made. For the first, second, and third born children the IQ is above average and almost equal. But in fourth, fifth, sixth (and up) children there is a steady drop in IQ to 103.78 for the children of grand multiparas (gravidia vi and up). Personality ratings do not follow the same pattern. The surprising drop in IQ with increasing parity could be misleading if the poorer classes with supposed lower IQ are the only ones having 4 or more children. Therefore, a group of 44 first, second, and third born children known to come from families of four or more children were studied and found to have an average IQ of 109.93; comparing this with the parity table, they fit between the fourth and fifth born children, suggesting that larger families do average a lower IQ, but parity does have some effect as these first, second, and third born children have a higher IQ than fifth or later born children. Similarly, a group of 94 siblings were studied with these rather confusing results:

- 13 children of primiparas had IQs 13.32 points higher than siblings.
- 10 children of primiparas had IQs 11.16 points lower than siblings.
- (Averaging these two groups, IQ of children of primiparas is 2.68 points higher.)



estrogenic hormone with large doses of riboflavin. While no change was observed after four to six weeks of treatment, more prolonged administration was followed by disappearance of these cells from the smears. Four cases have shown the same response. Only brief mention will be made here of these studies which are in a preliminary stage.

One of these cases, that of Mrs. L, aged 31 years, was cytologically diagnosed as precancer cell complex. The patient was treated for four months with a massive dosage of an estrogen combined with a heavy dosage of riboflavin. The precancer cells finally disappeared and could no longer be detected in the surface-biopsy smear. Following the cessation of the hormonal therapy, withdrawal bleeding was persistent, and while a curettage was performed a ring biopsy was also obtained for tissue study of the squamous tissue at the junctional area. The tissue showed no evidence of abnormal growth. Of course, it must be admitted this case was diagnosed initially by cytology and did not have an initial biopsy. It was felt that a biopsy might have removed the entire growth.

Such isolated case studies provide inadequate but still provocative evidence that we are dealing with a very early stage in the history of cervix cancer, using a method permitting study of cellular response and behavior. Statistics have been found difficult to collect or evaluate at the present early stage, although a few comparative figures are presented.

Variation has been noted in different selected groups, for example, in the in-hospital and gynecological clinic group of 1,300 patients, forty-five precancers have been diagnosed during an interval when thirty-six cervix cancers were found. (It should be explained that this includes patients referred to the cancer clinic as well as those attending the free gynecological clinic.) The average age of the precancer group is 40.8 years, while that of our cancer patients was 46.8 years.

In another outside (screening) group the incidence was lower. In 2,318 cases, sixty-four precancers were "called" to one hundred cancers. (High cancer incidence was accounted for on the basis that many of these tests were mailed to us as definite suspects.)

### Summary

Papanicolaou's vaginal smear technique has been described as a major advance in uterine cancer diagnosis. A modification of this technique, the surface-biopsy cervical scraping has been found especially useful in preclinical cancer by enabling evaluation of growth potentialities in the cells of the squamous margin of the squamocolumnar junction. Cells scraped from this vulnerable zone are described and classified into four groups: normal, inflammatory, precancer cell types, and cancer cells.

The precancer cell complex, a group of cells of borderline nuclear morphology, has been described and representative photomicrographs presented.

Behavior studies on a selected group of cases showing cells of precancer type are presented. Seven cases are briefly presented. Six cases showed progression from a precancer cell type to a cancer cell type over periods varying from six to eighteen months. In five of these, the lesions terminally were confirmed by surgical biopsy. One case showed cells of precancer type without progression, persisting after eighteen months. No case of spontaneous regression to normal was observed during this time.

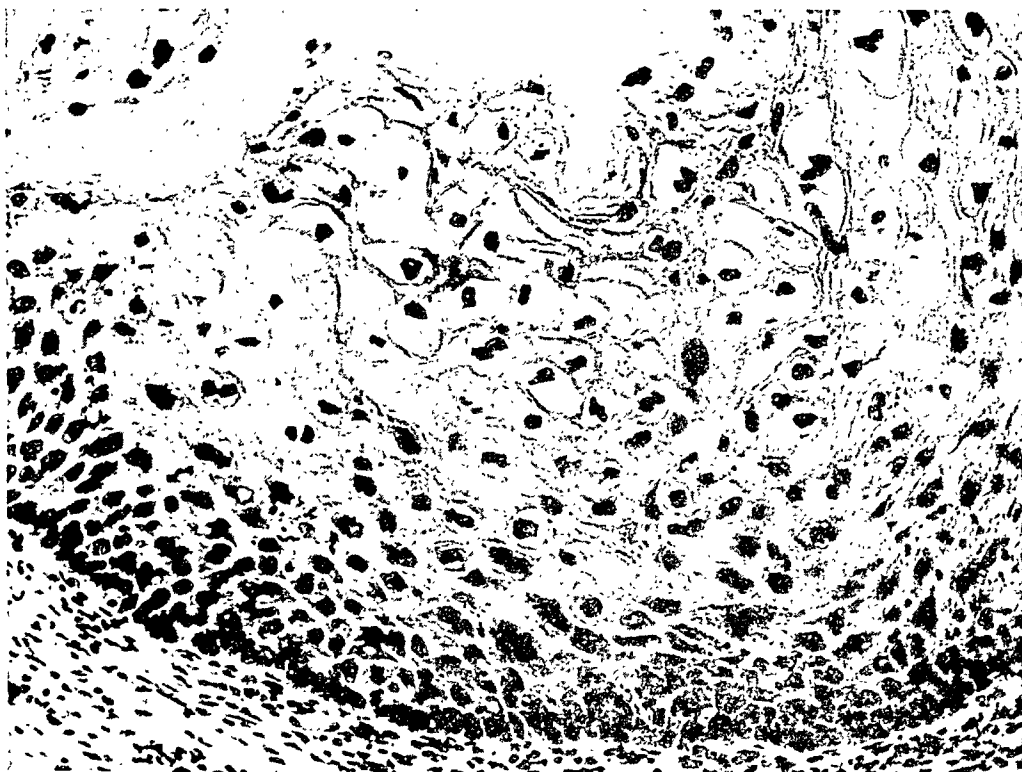


Fig. 12.—Cervical biopsy showing cells of precancer type in tissues. This section of tissue was adjacent to an area showing actual squamous carcinoma.



Fig. 13.—Cervical biopsy from the squamocolumnar region in another case showing many cells of the "precancer-cell complex" type. Throughout the tissue no further evidence of carcinoma was demonstrable in following thorough biopsy studies.

# Department of Reviews and Abstracts

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## Selected Abstracts

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### Cesarean Section

Pedvis, S., Irwin, J. K. L., and Philpott, N. W.: Fetal Mortality and Morbidity in Cesarean Section, *Surg., Gynec. & Obst.* 88: 103, 1949.

The authors have attempted an analysis of infant mortality in 353 cesarean sections with 357 infants resulting. The operations were performed in three different periods: from July 1, 1940, to Dec. 31, 1949; from July 1, 1944, to July 1, 1945; and from Jan. 1, 1946, to Dec. 31, 1946. These three periods were chosen in order to study three different types of anesthesia: namely, general, spinal, and local. The infants were classified as normal (those who were perfectly well both at birth and discharge); morbid (those who required prolonged resuscitation or had respiratory difficulties during the first twenty-four to forty-eight hours); and dead (nonviable infants, stillborn infants, and infants who died shortly after birth). The gross fetal mortality in this series was 7.3 per cent and the morbidity 11.2 per cent; 36.6 per cent of the deaths were due to prematurity, while 29.3 per cent were caused by atelectasis. A statistical analysis of the deaths in the different anesthetic groups is attempted. There seems to be no statistical difference in the number of infant deaths in the various anesthetic groups. However, such an analysis appears invalid, because of the varied and uncontrollable maternal complications which contributed to the deaths. Similarly, an attempt is made to determine statistically the influence of the various types of premedication in the causation of infant death. Statistically, there is no difference. Moreover, such statistical analysis is again invalid for the reason mentioned above. A special type of management for cesarean section babies is suggested and an attempt made to justify such management statistically. There is no statistical difference between the group submitted to special management and that without special management.

L. M. HELLMAN.

Shaw, Wilfred: Vaginal Operations for Cystocele, Prolapse of the Uterus, and Stress Incontinence, *Surg., Gynec. & Obst.* 88: 11, 1949.

The author describes in detail the anatomical relations of the endopelvic fascia in the vicinity of the anterior vaginal wall. There is a condensation of the endopelvic fascia behind the urethra. At operation no precise plane of cleavage is found between the vaginal and vesical fascial layers. In the operations used by the author for cystocele, prolapse, and vaginal hysterectomy, this fascia (which he terms the "post-urethral ligament") plays a most important part. In the operation for cystocele, the bladder is freed in the usual manner, the posturethral ligament is then brought down and sutured to the anterior surface of the cervix, the rest holding up the bladder. This key suture is also used in the Manchester-Fothergill operation. In vaginal hysterectomy, the ligament is used to support the anterior portion of the peritoneum, as well as the round ligaments on either side. Stress incontinence is treated by utilizing a sheet of fascia lata as a sling beneath the urethra. The two ends of the sling are brought up through holes bored in the pubic bone and sutured anteriorly. At the time of publication the author had treated twenty-five patients in this manner with satisfactory results.

L. M. HELLMAN.

Experimental therapy to precancer cases has been attempted. A group of cases is presently under observation. One of those is described in whom precancer cells disappeared following prolonged administration of massive doses of an estrogenic-riboflavin combination.

Diagrammatic representation of the localization of cancer cells, precancer cell types, and normal cells in early microscopic cancers is attempted.

The cytological method is visualized as opening up a valuable new field of approach for diagnosis and for behavior studies of lesions believed to represent the formative stage of cancer.

The author wishes to express sincere appreciation to Dr. Robert Chambers and Dr. W. Burton Ayre for assistance in the interpretation and evaluation of cells classified as of precancer type; to Dr. J. S. Henry and Dr. W. A. G. Bauld and other Staff Members of the Department of Gynecology and Obstetrics of the Royal Victoria Hospital, who have co-operated in making possible the careful follow-up on cases diagnosed as precancer. Appreciation is due also to Miss Evelyn Dakin, Director of Technicians, and to the entire Technical Staff who have cooperated in the preparation of this work.

This work was assisted by a grant from the Public Health Foundation for Cancer and Blood Pressure Research, New York.

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MacFarlane, Catherine, Sturgis, Margaret C., and Fetterman, Faith S.: Control of Cancer of the Uterus, J. A. M. A. 138: 941, Nov. 27, 1948.

The authors report their findings on 732 volunteers who have been examined more or less regularly over a period of 10 years. Eight cancers of the pelvic organs were discovered in the group of 732 volunteers over this ten-year period. The authors continue to stress the importance of periodic pelvic examination, especially on women past 30 years of age who have had one child.

WILLIAM BERMAN.

and straining will initiate some descent of the internal sphincter but the sphincter itself being in good tone no urination occurs. In the incontinent individual relaxation of the pubococcygeus muscle allows the base of the bladder and the internal sphincter to descend during each period of coughing or straining. With some slight relaxation of the sphincter, the descent of the bladder is enough to initiate urination.

L. M. HELLMAN.

Ball, Thomas L., and Javert, Carl T.: Fertility and Dysgerminoma Ovarii, *J. Clin. Endocrinol.* 8: 694, 1948.

This communication briefly reviews the literature in which pregnancy associated with or following dysgerminoma of the ovary is discussed. In the largest series of cases tabulated by Seegar the fertility rate was 23 per cent.

A case is reported in which a 39-year-old primigravida was delivered by midforceps of a male infant weighing 2,900 Gm. Examination of the infant revealed a first degree hypospadias, there were no other abnormalities noted.

The patient herself gave a history of having been operated upon twelve years earlier and, at that time, a right salpingo-oophorectomy was done for a solid tumor of the right ovary. Postoperatively, four x-ray treatments were administered. The exact dosage was not determined; however, it was stated that the left ovary was protected with a lead screen. Since the patient did not cease to menstruate after the radiation therapy, the amount of radiation that reached the left ovary was not enough to cause castration. The slides from the original tumor were reviewed by the present authors and the diagnosis of dysgerminoma was clearly established. A plea is made for conservatism (unilateral oophorectomy when only one ovary is involved) in cases of dysgerminoma in spite of the anaplastic character of the tumor.

HERBERT J. SIMON.

### Menstruation, Dysmenorrhea

Davis, M. Edward, and Fugo, Nicholas W.: The Cause of Physiologic Basal Temperature Changes in Women, *J. Clin. Endocrinol.* 8: 550, 1948.

It is now generally accepted that the basal body temperature in the normally menstruating woman is biphasic in character. In this communication the authors have made studies to determine the cause of this phenomenon. An analysis of well over 1,000 temperature graphs showed that 75 per cent of patients present a curve which, when properly interpreted, will give exact information as to the time of ovulation. Emotional, physical, and metabolic stimuli in themselves cause irregular temperature fluctuations in the remaining 25 per cent and thus mask the normal curve.

In a study of one hundred basal temperature graphs of women who conceived, seventy-two were known to have had coitus at least once during the period of the temperature rise or at its peak. It is thought that the high level of the temperature during the luteal phase of the cycle is caused by progesterone. The fact that the authors were able to recover from the urine increased amounts of pregnandiol during the period of elevated temperature supports this view. Twenty-four to thirty-six hours prior to the onset of the menses, the activity of the corpus luteum ceases, the pregnandiol levels drop, and the temperature curve returns to the preovulatory level. If pregnancy occurs there is no drop in temperature, whereas in an anovulatory cycle, there is no rise in temperature. All this substantiates the theory that progesterone is the cause of the temperature shift. The authors were able to bring about a typical temperature rise in two groups of young women without ovarian activity. In the first were four young women with primary amenorrhea, and the second included four young women who had been subjected to surgical castration and hysterectomy for pelvic disease. In both these groups the method employed was a daily oral dose of 0.3 mg. of ethinyl estradiol. Then, at the end of about two weeks, 10 mg. of progesterone in oil were administered intramuscularly daily in ad-

## Endometriosis

Kelly, Francis J., and Schlademan, K. Ramsay: Endometriosis, Its Surgical Significance. A Critical Analysis of 79 Cases, Surg., Gynec. & Obst. 88: 230, 1949.

During 1,991 consecutive abdominal gynecologic operations, the authors encountered 79 histologically verified cases of endometriosis. These represent the basis of this paper. Acquired dysmenorrhea was present in 48.2 per cent of the cases, while dysmenorrhea of increasing severity was present in 33.5 per cent. One of the most striking features of endometriosis is its relation to fertility. Using a normal fertility rate of 88 per cent, the authors found that the absolute fertility rate for the series under consideration was 46.4 per cent. Though radical operative procedures were considered necessary in the majority of these cases, the authors felt that conservatism was justified when possible as indicated by an absolute fertility rate of 23.7 per cent after conservative surgery. L. M. HELLMAN.

## Extrauterine Pregnancy

Karsh, Jamil: Abdominal Pregnancy Following Rupture of Cesarean Scar, Canad. M. A. J. 60: 70, 1949.

A young secundigravida, previously delivered by cesarean section, developed term labor lasting about three days, followed by five weeks of diffuse abdominal pain, which gradually subsided. Vaginal bleeding appeared in the third week, and persisted for two months. Thereafter, she had regular menses for eight months, followed by irregular vaginal bleeding and discharge, with low grade sepsis, for four months. At laparotomy, the degenerating ovum was surrounded by a thick adherent fibrous capsule. The uterus was of normal size, with a gaping ruptured cesarean scar. Hysterectomy was done. IRVING L. FRANK.

## Gynecology

Muellner, S. Richard: The Etiology of Stress Incontinence, Surg., Gynec. & Obst. 88: 237, 1949.

In a previous study the author made an attempt to determine the lesion responsible for stress incontinence by examining ninety-five patients with exertional incontinence and forty-five continent multiparas using cystometry, cystoscopy, cystography, and urethrog-raphy. These studies all failed to revealed a specific lesion. During the past year eighty-five observations have been made using a fluoroscopic technique, thirty of these on women suffering from stress incontinence. These studies were carried out with the bladder filled with a contrast medium of 5 per cent sodium iodide to which 20 c.c. of aqueous Diodrast had been added. Usually 200 to 250 c.c. of the solution were sufficient. Observation was then made through the fluoroscope with the patient standing and supine. Care was always taken to maintain the relationship of the x-ray tube and the symphysis so that changes in the position of the bladder resulting from change of posture could be accurately evaluated. Spot films were also taken from time to time. In the normal nullipara, while recumbent, the bladder has a smooth outline. When she coughs, the base of the bladder does not yield, but the impulse on the increased intra-abdominal pressure is dissipated along the dome and the sides of the bladder. When she is asked to void, the base of the bladder can be seen to descend sharply so that the region of the internal sphincter becomes the most dependent portion and assumes a pointed appearance. This is the first important maneuver in the complex process of micturition. It is this descent of the internal sphincter which opens it slightly and permits a small amount of contrast medium to enter the proximal urethra. If such a subject is asked to inhibit the urinary stream, she pulls the base of the bladder up to a level slightly higher than it had assumed before micturition. In a continent multipara, the events are very similar except that the bladder is somewhat larger and flabbier and the bladder supports more yielding. In the continent multipara, coughing

and after treatment averaged twenty-nine to thirty days. In all cases but one, endometrial biopsy showed secretory endometrium just before the onset of the period.

A group of five women complaining of dysmenorrhea was similarly treated. The 20 mg. dose of stilbestrol did, however, cause an anovulatory cycle in one patient. The authors conclude (with previous workers) that a single large dose of estrogen given early in the menstrual cycle will delay but not inhibit ovulation and thus increase the length of the cycle.

Another group of five dysmenorrheic women was given stilbestrol over a period of thirty days, beginning at the end of the period. One mg. of stilbestrol was given daily for the first ten days, 2 mg. daily for the second ten days, and 3 mg. daily for the third ten days. Anovulatory bleeding occurred usually three days after the last dose and the patients were relieved of their painful menses. This was continued for three successive cycles without apparent ill effect.

In a final series of six patients, stilbestrol was given in the postovulatory phase of the cycle. The luteal phase was not prolonged, the progesterational endometrium was normal, and there was no increase in the length of the cycle. It would thus appear that the human corpus luteum, once formed, is not affected by the administration of estrogen.

HERBERT J. SIMON.

Macpherson, Cluny: Pelvic Allergy, Canad. M. A. J. 60: 54, 1949.

Excellent, and sometimes dramatic, results are reported with the use of Adrenalin chloride hypodermically (1 c.c. of 1:1000 solution), as emergency treatment in cases of severe functional dysmenorrhea. Recently the author has used Benadryl (50 mg.) to be taken thrice daily on the premenstrual day, with good results in preventing menstrual pain.

IRVING L. FRANK.

### Miscellaneous

Waksman, Selman A., and Lechevalier, Hubert A.: Neomycin, a New Antibiotic Active Against Streptomycin-Resistant Bacteria, Including Tuberculosis Organisms, Science 109: 305, March 25, 1949.

The authors report a new antibiotic produced by *Streptomyces faradiae*. The organisms are grown on a medium containing nitrogen, carbohydrates, and salt. The antibiotic is easily removed from the medium and concentrated by methods previously developed for the isolation of streptothricin and streptomycin. It has been termed by the authors Neomycin, and is a basic compound most active in alkaline solution. It is soluble in water and insoluble in organic solvents and thermostable. It has proved active against numerous Gram-positive and Gram-negative organisms, and especially the mycobacteria. The antibiotic spectrum of crude Neomycin is distinct from streptomycin and streptothricin. It is particularly active against streptomycin-resistant bacteria and possesses considerably more activity against *Mycobacterium tuberculosis*. It has limited or no toxicity in animals. Neomycin has not yet been obtained in crystalline form and therefore little can be said concerning its chemical nature.

L. M. HELLMAN.

de Soldenhoff, Richard: Early Ambulation in Obstetric and Gynaecological Cases, Lancet, p. 961, Dec. 18, 1948.

The author discusses his experiences with early rising in 1,611 obstetric and 212 gynecologic cases. Puerperal women are permitted to sit up in bed six to eight hours after delivery, and are allowed out of bed with lavatory privileges on the third postnatal day. A two-step platform is provided to reaccustom patients to stair climbing. Cesarean patients follow the same routine. The now familiar advantages of this regime are described.

IRVING L. FRANK.

dition to the ethinyl estradiol, for twelve to fifteen days. The only variation from the temperature curve of normal women was that there was a more abrupt rise and a slower fall of the temperature. In a group of twelve women, the ovarian function following surgical removal of the uterus was studied. Cyclic elevation of the temperature associated with increased pregnandiol excretion was found. It would, therefore, appear that the uterus is not essential for a normal hormonal cycle.

In order to explain the fact that conception often occurs during a temperature rise, it is suggested that the theca-interna cells excrete progesterone prior to actual ovulation. It may, therefore, be postulated that ovulation takes place during the temperature rise rather than, as was formerly believed, just before the rise.

HERBERT J. SIMON.

Buxton, Charles L., and Atkinson, William B.: Hormonal Factors Involved in the Regulation of Basal Body Temperature During the Menstrual Cycle and Pregnancy, *J. Clin. Endocrinol.* 8: 544, 1948.

In this communication the actual cause of the temperature rise during the latter half of the menstrual cycle and the progress of the basal body temperature during pregnancy are presented.

Six patients with secondary amenorrhea and lack of ovarian function as determined by endometrial biopsy were selected for study. A temperature base line was established and then a priming dose of estrogen was given daily for about two weeks. Immediately thereafter 10 to 25 mg. of progesterone were administered daily from seven to fourteen days. The estrogen produced a slight depression of the basal temperature whereas the progesterone caused a rise up to a degree or more. Endometrial biopsies confirmed hormonal activity. The postovulatory temperature rise in normally menstruating women can be maintained by the administration of large amounts of chorionic gonadotropins. It would appear that the chorionic gonadotropin stimulates the corpus luteum to produce progesterone which in turn causes the rise in temperature. To prove that chorionic gonadotropin is not directly responsible for the maintenance of the temperature rise, an equivalent amount was given, after estrogen priming, to a 31-year-old bilaterally ovariectomized woman. No rise in temperature resulted.

It would be expected that the elevated body temperature would continued throughout pregnancy since there is an apparent increasing amount of progesterone as determined by the pregnandiol excretion. Three patients kept temperature charts throughout their period of gestation. In each case there was a gradual drop of the temperature to the preovulatory levels during the fourth month. To explain the discrepancy between the apparent rise in the progesterone as indicated by the increase in pregnandiol excretion and the fall in temperature, it is predicated that a refractory state develops in which the thermogenic action of the progesterone is overcome by thermodepressant factors. A second theory suggests that a lytic activity of the trophoblast on the decidua of the mother during the early months of pregnancy results in a slight febrile response. An additional explanation to account for the fall in basal body temperature as pregnancy progresses assumes a diminished physiologic activity of the progesterone.

HERBERT J. SIMON.

Brown, Willis E., Bradbury, J. T., and Jennings, A. F.: Experimental Alteration of the Human Ovarian Cycle by Estrogen, *J. Clin. Endocrinol.* 8: 453, 1948.

This study was undertaken in order to demonstrate any alteration in the human menstrual cycle caused by the administration of estrogen. The corresponding ovarian cycle was followed by weekly endometrial biopsies.

In the first series of six normal patients, a single dose of 20 mg. of stilbestrol was given early in the menstrual cycle (fourth, fifth, or sixth day). The result was prolongation of the interval to thirty-eight days. In this group of patients, the intervals before



profuse hemorrhage three times; recurrent slight bleeding for one to four weeks followed by moderate, profuse hemorrhage fifteen times; recurrent slight bleeding for four weeks to four months followed by moderate profuse hemorrhage seven times; initial moderate bleeding followed in one to six weeks by second moderate to profuse hemorrhage seven times; one episode of bleeding in the seventh month, once. The first instance of hemorrhage occurred during labor five times. The authors feel that vaginal or rectal examination should not be performed in the home nor in suspected cases should it be done in the hospital until one decides to terminate the pregnancy at about the thirty-eighth week. Tamponade and dilating bags are obsolete and version nearly so. Interference from below should be restricted to simple rupture of the membranes or, in case of a frank breech in a multipara, an easily accessible limb may be pulled through the cervix. Great care should be taken with the placental stage of delivery, with a view to prompt manual removal if placental bleeding should continue. Finally, the authors feel that the expectant treatment of placenta previa is safe under proper conditions. They emphasize, however, that the patient should remain in the hospital during the period of expectancy.

L. M. HELLMAN.

Switzer, Paul K., and Fouche, Heyward H.: The Sick Cell Trait: Incidence and Influence in Pregnant Colored Woman, *Am. J. M. Sc.* 216: 330, 1948.

The authors differentiate clearly between sickle cell anemia in which there is sickling of the red cells but no blood destruction or increased rate of regeneration, and true sickle-cell anemia in which there is sickling as well as active blood destruction and increased regeneration as evidenced by reticulocytosis and nucleated red cells. There are numerous reports in the literature of true sickle-cell anemia associated with pregnancy; however, there have been no studies made of the occurrence of pregnancy in patients with sickle cell anemia nor of the effects of pregnancy on such patients. Five hundred consecutive Negro women who were pregnant were examined for sickling. In addition, two hundred fifty nonpregnant Negro women of childbearing age and two hundred fifty Negro men were also studied. There was an incidence of sickling of approximately 14 per cent in all three groups. The sickling trait did not interfere with conception nor had it any apparent deleterious effect on either the pregnancy or the labor in any of the pregnant women. One patient had active sickle-cell anemia of a mild type. It was not known whether this existed prior to her pregnancy. In twenty-two patients with sickle cell anemia studied in the hospital, the pregnancy did not initiate a blood-destructive process.

HERBERT J. SIMON.

### Pregnancy, Physiology

Black, Elinor F. E.: Diuretic Effects of Estrogens in the Last Four Months of Pregnancy, *Canad. M. A. J.* 59: 431, 1948.

The author presents a series of forty cases of excessive weight gain in pregnancy, 77.5 per cent of which responded satisfactorily to the administration of small doses of estrogens. The author divides weight gain in pregnant women into three groups: those who go through the nine months with a normal weight gain; second, those who gain weight rapidly with onset of edema and later develop hypertension and albuminuria; and third, those who gain excessively throughout pregnancy despite restrictions in diet, salt and fluid intake, yet develop no edema and no other evidence of toxemia. The administration of estrogens as a method of limiting excessive weight gain during pregnancy is apparently free from deleterious effects on the patient and the fetus. Twenty-nine of the forty patients showed a satisfactory response to estrogen therapy. Five patients showed a poor response. Two patients showed an added weight increment during the course of estrogen therapy. It is felt that the clinical results that have been observed suggest that further investigation and assessment of the role of the estrogens in the matter of fluid retention are warranted.

WILLIAM BERMAN.

## Newborn

Chapman, Earle M., Corner, G. W., Jr., Robinson, David, and Evans, R. D.: The Collection of Radioactive Iodine by the Human Fetal Thyroid, *J. Clin. Endocrinol.* 8: 717, 1948.

This study corroborates the theory that the human fetal thyroid probably begins to function at about four and one-half months.

Radioactive iodine was administered to nine pregnant women who were to be operated upon forty-eight hours later for the termination of pregnancies which endangered their lives. It was found that the thyroid tissue of 7- to 12-week fetuses exhibited no radioactivity. In those aged from 14 to 32 weeks, the radioactivity tended to increase with increasing age. Histologic studies suggested that the onset of thyroid function is associated with the appearance in the gland of definite follicles containing colloid.

From this study it would appear that toxic goiter in pregnant women may be treated by radioactive iodine up to the fourth month of pregnancy without effect on the thyroid of the fetus.

HERBERT J. SIMON.

Norman, R. M.: Cerebral Diplegia Following Birth Injury, *Bristol Med.-Chir. J.* 65: 43, 1948.

In nine cases of cerebral diplegia a detailed examination of the brain was made. All of these nine patients were firstborn and eight were boys. There were two twin births. In four cases the birth weight was low,  $4\frac{1}{2}$  to  $5\frac{1}{2}$  lb. The birth was rapid in two of these cases and precipitate in one case. In one case there was dry labor with a post-mature infant; in another, the mother was known to have a pelvic contracture. In every case the birth history was abnormal or suggestive of intracranial damage. Three infants showed severe asphyxia; two showed apathy with inability to take the breast; three had twitching of the limbs during the first few days of life. During life, six of these patients had a symmetrical spastic paresis of the limbs with contractures of hamstrings and adductors and signs of upper neurone deficiency; two had a hemiplegia with contractures and a less severe spastic paresis of the leg on the opposite side; in one case there was rigidity of the extrapyramidal type with associated athetosis. Epilepsy developed in six cases. The lesions found at post-mortem examination were of two main types: (1) lesions of the cerebral cortex which were attributable to hemorrhage from or stasis in veins draining into the superior longitudinal sinus; (2) lesions of the central white matter of the brain and basal ganglia often symmetrically placed which were attributable to hemorrhage or circulatory stasis in areas drained by the tributaries of the great vein of Galen.

HARVEY B. MATTHEWS.

## Pregnancy, Complications, Toxemia

Gordon, Charles A., and Rosenthal, Alexander H.: The Expectant Treatment of Placenta Previa. A Study of 50 Maternal Deaths, *Surg., Gynec. & Obst.* 88: 259, 1949.

In a study of 1,011 maternal deaths occurring in Brooklyn in the ten-year period from 1937 to 1947, 145 were officially assigned to hemorrhage. Placenta previa was associated with deaths in fifty instances. In these fifty cases of placenta previa, twenty-five patients were delivered pelvically, while twenty-two were delivered by cesarean section. The major cause of death was infection, which occurred in eighteen cases. Hemorrhage was responsible for death in fifteen cases, while rupture of the uterus occurred eight times. The pattern of hemorrhage showed considerable variation in time of onset, amount of initial hemorrhage, and character of recurrent bleeding. Initial profuse antepartum hemorrhage occurred twelve times; spotting for four or five weeks followed by moderate or

14 children of multiparas had IQs 14.14 higher than younger sibling.  
 18 children of multiparas had IQs 16.29 lower than younger sibling.  
 (These two groups average 2.98 points lower for older sibling.)

TABLE VII. EFFECT OF PARITY

GRAVIDA	IQ	PERSONALITY RATING	NUMBER OF CASES
1	112.53	2.55	147
2	112.17	2.36	94
3	113.8	2.41	48
4	110.72	2.41	25
5	108.81	2.33	24
6 and over	103.78	2.73	39

Two other factors not investigated were suggested by one infant who had bloody spinal fluid, having an IQ of 67; and by another whose mother had threatened to miscarry but successfully delivered a child whose IQ was later found to be 79.

### Summary and Conclusions

An infant's IQ may be affected by factors related to pregnancy, labor, and the infant himself.

The pregnancy factors are as follows:

1. Eclampsia was found to result in IQ of 101.2.
2. Pre-eclampsia resulted in IQ of 105.89.
3. Maternal weight gains over 25 pounds progressively lower IQ (to 105.3 if mother gains over 35 pounds).

The factors of labor are as follows:

1. Labors over 30 hours result in IQ of 102; labors under one hour result in IQ of 105.8.
2. Increasing multiparity is associated with lower IQ, grand multiparas having children with IQ of 103.78.
3. Cases probably receiving Pituitrin had children with IQ average of 105.11.
4. Ether anesthesia resulted in IQ of 107.67.
5. Forceps deliveries resulted in IQ of 109.51.

Infant factors are as follows:

1. Weight: Babies over 5 through 6 pounds had an IQ of 105.24.  
           Babies over 9 pounds had an IQ of 108.8.
2. Sex: Male IQ, 108.2; Female IQ, 112.12.

The IQ for the entire series was 110.04.

## Puerperium

Norrish, R. E.: Residual Dilatation of the Upper Urinary Tract Following Pregnancy, *Practitioner* 161: 47, 1948.

It has long been recognized that there are changes in the form of the renal pelvis and ureter during pregnancy, although the cause of these changes is still a matter of discussion. These changes are associated with urinary stasis and predisposition to infection, as shown by the frequent occurrence of pyelitis in pregnancy. In uncomplicated cases return to normal form and tonus of the ureter and bladder occurs about the sixth week after delivery. This may be delayed by the presence of infection, and there may be some degree of residual dilatation. This residual dilatation may be maintained by subsequent pregnancies until the ureter becomes stiffened by fibrosis and the pelvis atonic, a condition that may persist after the childbearing period. Four illustrative cases are presented (with pyelograms). In the first case, the ureters and renal pelvis returned to normal by the eighth week after delivery. In the second case only the right ureter was dilated during pregnancy and there was no infection; the condition cleared up completely. In the third case the patient was 52 years of age; she had had six children; pyelitis had occurred in her first pregnancy and recurred in each subsequent pregnancy. For many years after her last pregnancy she continued to have backache, dysuria, and increased frequency; and examination showed a coliform urinary infection. Intravenous pyelography showed the right ureter and pelvis dilated, with kinking and twisting of the ureter, as is often found in pregnancy. In the fourth case the patient had had two pregnancies, with the urinary infection during the first pregnancy, which had persisted intermittently. During an exacerbation of symptoms, intravenous pyelography showed the right renal pelvis and ureter to be much dilated. When she became pregnant again a few months later, pyelograms showed dilatation of the ureter and pelvis on both sides. Four months after delivery the left ureter and pelvis were normal, but dilatation persisted on the right side and urinary infection was still present.

HARVEY B. MATTHEWS.

Doyd, David A., Jr., and Brown, De Witt W.: Electric Convulsive Therapy in Mental Disorders Associated With Childbearing, *J. Missouri M. A.* 45: 573, 1948.

Most mental disorders associated with childbearing occur after delivery and are characterized by manic-depressive and schizophrenic reactions. Experience with electroshock in major psychoses (nonpuerperal) indicate that it is most effective in cases with a strong depressive trend, less effective in manic patients, and least beneficial in schizophrenia. A review of the cases reported in literature of puerperal psychoses treated with electroshock, and the authors' own experience indicate that the same is true in the puerperal psychoses. The fact that electroshock has proved effective in a large percentage of cases of puerperal psychosis may be attributed to the fact that many of these psychoses show a strong depressive trend. While some therapists consider that electroshock treatment should not be given during the first month after delivery, other therapists have found that the prompt use of electroshock therapy is markedly effective and shortens the duration of the illness. In the authors' cases of postpartum psychosis, psychiatric indications for electroshock therapy have been the deciding factors as to whether it is to be used and when it is to be given. As soon as routine psychiatric and physical examinations have been completed, and electroshock has been found to be definitely indicated, this treatment is begun. In the authors' cases, therapy was instituted on the twenty-second, twenty-fourth, and fourteenth days after delivery, respectively. Two cases of puerperal psychosis are reported in which good results were obtained.

Manic-depressive and schizophrenic psychosis occurring during pregnancy are dangerous to both the mother and the child; delay of treatment of the psychosis until after the termination of the pregnancy may render the psychosis irreversible. Electroshock

therapy has not been found to be dangerous to the mother or to cause termination of the pregnancy, as shown by the cases reported in literature. It often makes it possible to carry the patient to term and at the same time to improve her physical as well as mental condition. The treatment is begun as soon as the diagnosis and the indications for electroshock therapy are established. Two cases of electroshock therapy during pregnancy are reported. In one of these cases the pregnancy was far advanced when treatment was begun in order to relieve uncontrolled excitement that threatened the lives of both the mother and the child; in this case the child was delivered prematurely, but lived and grew normally; the mother required further electroshock treatments in the puerperium, but made a complete recovery.

HARVEY B. MATTHEWS.

Dunlap, John C., and Diddle, A. W.: Comparative Effect of Synthetic Estrogenic Substances on the Postpartum Breast, *J. Clin. Endocrinol.* 8: 880, 1948.

In this paper the effectiveness of dienestrol is compared with diethylstilbestrol and alpha estradiol in preventing engorgement of the postpartum breasts of nonnursing mothers. The authors' results show that alpha estradiol was frequently ineffective, whereas, with dienestrol and diethylstilbestrol, engorgement was more often averted. They further found that engorgement recurred less frequently after administering dienestrol than after diethylstilbestrol. None of the drugs used appeared to cause any increase in the lochia rubra. The authors call attention to the fact that breast engorgement and lactation are apparently independent of one another. The former is caused by lymphatic and vascular stasis, not by distention with milk. The flow of milk is stimulated more by suckling than by any hormonal action; hence, when it is desired to dry up the breasts, it is unwise to massage or empty them.

HERBERT J. SIMON.

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## Items

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### Increase in Size of the Journal

Our readers are notified that, beginning with the January issue, the JOURNAL will be enlarged to a total of 232 pages of reading matter. See announcement on page 28 of the advertising section of this number.

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### Clinical Assembly

The Fifth Annual Midwinter Clinical Assembly in Obstetrics and Gynecology given by a group in Southern California will be held during the week of February 13 to 18, inclusive. For further information apply to

DR. GEORGE E. JUDD,  
1930 Wilshire Boulevard,  
Los Angeles 5, Calif.

# Correspondence

## Rh Sensitization

To the Editor:

In answer to many questions addressed to me, raised by an article on "Rh Sensitization in a Primipara Caused by Intramuscular Injection of Human Serum Resulting in Fatal Erythroblastosis" by Wallace, Wiener, and Doyle, published in THE AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, December, 1948, this unfortunate publication has confused and disturbed a considerable number of physicians, particularly obstetricians, several of whom have written me about it. The idea that *clear* serum or *clear* plasma may produce Rh sensitization when injected into a human being who is Rh negative, particularly a woman who subsequently bears an Rh-positive child, is not supported by careful analysis to date. This single case report is entirely unconvincing and I believe it has frightened both physicians and laymen quite unnecessarily.

It is known, and we have proved repeatedly in the Blood Grouping Laboratory of Boston, that even minute doses of whole blood or red blood cells, as little as one-tenth of 1 c.c., repeated on several occasions, may sensitize an Rh-negative individual. Between 50 and 60 per cent of our experimental group of Rh-negative males receiving such injections of Rh-positive cells eventually develop Rh antibodies. There is the possibility, therefore, that during the injection of serum or plasma if intact red cells are present in the liquid (which not infrequently occurs and in the past has not been carefully avoided) an Rh-negative person might receive a stimulating or sensitizing dose. However, if the plasma or serum is carefully prepared and no intact red cells are contained therein, there should be no concern about this possibility. We have tested the blood of several hundred Rh-negative men and women who have received both single injections and multiple doses of plasma intravenously and find no evidence of Rh sensitization in any of these to date.

In addition, we have verified cases of Rh-negative women who have begun developing Rh antibodies as early as the fifth week of gestation in a proved first pregnancy. We know from numerous tests that fetal blood contains Rh-positive red cells as early as the third or fourth week of gestation and, therefore, the possibility of transplacental sensitization from Rh-positive cells may exist in the Rh-negative women harboring an Rh-positive fetus even as early as the second month of gestation. In essence, therefore, it may be stated that the case report of Wallace, Wiener, and Doyle does not prove or even present a strong possibility that their patient was sensitized after an intramuscular injection of serum. Much more likely this was one of the rare patients in whom sensitization occurred due to pregnancy itself relatively early during a first gestation.

LOUIS K. DIAMOND, M.D.

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BOSTON, MASS.  
AUGUST 30, 1949

## Reply by Drs. Wallace and Wiener

To the Editor:

The letter by Dr. Diamond is most helpful since it has given us an opportunity to clarify certain points in our article "Rh Sensitization in a Primipara Caused by Intramuscular Injection of Human Serum Resulting in Fatal Erythroblastosis."

1. While a single injection of compatible blood is sufficient to cause a rise in titer of alpha and beta antibodies, a minimum of two properly spaced injections is required to bring about Rh sensitization. Group O individuals already have a background of sensitization

against the A and B factors as evidenced by the alpha and beta agglutinins normally present in the serum. The injection of group A blood into such individuals, therefore, brings about an anamnestic specific reaction so that there is a prompt rise in the alpha antibody titer. The normal Rh-negative individual has no such background of sensitization and must first be primed by an injection of Rh-positive blood or a pregnancy with an Rh-positive fetus. After a latent period of about three to four months or longer, the primed Rh-negative individual can usually be made to respond to a second contact with Rh antigen by the production of Rh antibodies.

2. Sensitization of Rh-negative individuals by injections of Rh-positive blood is successful in more than half the cases. Sensitization of Rh-negative individuals by Rh-positive fetuses occurs on the average in only one out of fifteen to twenty cases. This is obviously a question of *dosage*, because much more blood is introduced by injection than could leak across a placental barrier.

3. The most sensitive test for the presence of Rh antigen in a substance is to inject it intravenously into a primed Rh-negative person. When an Rh-negative person has once been sensitized and a sufficient interval of time has been allowed to pass, even a minute dose of antigen will bring about a substantial rise in antibody titer. Based on such indirect evidence it has become clear that fetal red cells leak into the maternal circulation most regularly at parturition, though this may also occur at any time during the pregnancy, even as early as the seventh week as in our case report, which is the subject of the present discussion.

4. Since a minimum of three to four months is necessary to prime an Rh-negative individual, and since our patient showed antibodies as early as the seventh week of gestation it is obvious that she must have been primed some time before the pregnancy began. The only exposure that could be elicited in the past history was the injection of pooled adult serum received at the age of eight years.

5. Even serum prepared in such a way as to avoid trauma to the red cells will contain some stromata in suspension from effete red cells. Certainly there have been and probably still are in some parts of this country laboratories whose facilities do not permit the "proper" preparation of serum and plasma. Further, such serum prepared from pooled blood, outdated blood, and centrifuged blood will contain significant quantities of stromata, and therefore Rh antigen, from hemolysis due to intergroup reactions, aging, and trauma. No doubt, rare Rh-negative individuals exist who could be primed by even such small amounts of antigen. It is quite possible, of course, that our case is extremely rare or unique just like other rare cases of sensitization to poor antigens like Hr<sub>0</sub>, hr'', etc. In any event, its unusual features made it important enough to report.

6. Dr. Diamond's studies on sensitization of Rh-negative patients by plasma injections are important. For the results to be of significance, however, it is necessary to show that at least two plasma injections were given to each subject at an interval of not less than three to four months.

7. That the principle of priming followed by a latent period of three to four months is probably correct follows from our successful application of the principle for the preparation of Rh antisera. While we often succeed with only two injections, other workers who ignored this principle have had to use multiple injections up to sixty in number before obtaining results.

8. Even if our case is exceptional, it seemed important to point out that the injection of pooled plasma or serum is not as harmless as commonly assumed. Pooling of serum also increases the chance of transmitting the virus of hepatitis, and of inducing A-B sensitization, which can give rise to erythroblastosis. Obviously, therefore, the therapeutic use of human serum and plasma requires more intensive investigation from the standpoint of the hazards associated with such injections.

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J. T. WALLACE

64 RUTLAND ROAD  
80 HANSEN PLACE  
BROOKLYN, N. Y.  
NOVEMBER 16, 1949

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# DIAGNOSIS AND MANAGEMENT OF RUPTURE OF THE UTERUS\*

## With a Study of 64 Maternal Deaths

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IN 1943 we<sup>1</sup> reported thirty maternal deaths from rupture of the uterus which had occurred in Brooklyn during the period, January, 1937, to September, 1942; fourteen additional cases in which this diagnosis was not proved, though highly probable, were not reported at that time. Since then, until January, 1948, twenty deaths from rupture of the uterus have occurred, eighteen of them proved. Since our first report presented but little clinical data, these thirty cases have been restudied and included in this series. The total number of cases, then, is sixty-four, in sixteen of which rupture of the uterus, though not proved, is believed to have occurred. All cases have been discussed by the Committee on Maternal Welfare of the Medical Society of Kings County.

In 48 cases the site of rupture was recorded. The upper segment ruptured in but 3 cases. In 45 cases rupture occurred entirely or principally in the lower segment, chiefly lateral, but in the anterior and posterior walls as well. In 16 cases in which rupture was not proved, it probably took place in the lower segment.

There were seven primiparas and 57 multiparas, with but one primipara in the spontaneous rupture group; 58 patients were white, and eight Negro.

On the basis of etiological factors, 27 are classified as spontaneous and 37 traumatic. Further subdivision follows:

### *Spontaneous Rupture.—*

"Grand multipara"	8 cases
Rupture of uterine scar	4 cases
Pituitary extract	4 cases
Obstructive dystocia, hydrocephalus	3 cases
Cervical scar	2 cases
Other	6 cases
	<u>27 cases</u>

### *Traumatic Rupture.—*

Version	20 cases
Forceps	9 cases
Craniotomy	3 cases
Fundal pressure	3 cases
Pinard maneuver	1 case
Bagging	1 case
	<u>37 cases</u>

## Spontaneous Rupture

The "grand multipara."—The eight women in this group showed great multiparity. Brief case reports follow. All were proved to be ruptures of the uterus save Case 1.

\*Read before the Brooklyn Gynecological Society, May 7, 1948.

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7. 1949 Palmer, Reinhard, Sadugor, and Goltz<sup>21</sup>

8. 1949 American College of Surgeons<sup>1</sup>

Heyman's<sup>14</sup> classification has 3 parts:

1. Clinically operable,
2. Technically operable, and
3. Inoperable.

Its simplicity recommends it.

Crossen's classification is:

Stage I. Endometrium alone involved.

Stage II. Definite involvement of muscular wall, but not beyond its middle.

Stage III. Extension to the outer half of the uterine wall, but not beyond the borders of the uterus. This includes extension to the peritoneal coat with possible areas of adhesive peritonitis, but without carcinomatous involvement of the adhesions.

Stage IV. Extension to surrounding structures, but not beyond removable ones, such as adnexa and adjacent portions of the broad ligament. There may or may not be extensive intestinal or other peritoneal adhesions, but no extension of carcinoma cells into such adhesions.

Stage V. Extension into structures which it is not advisable to remove, but removal of original tumor is still practicable. The carcinomatous extension may be into an adherent coil of intestine or an adherent area of bladder wall, or it may be along the broad ligament lymphatics into the deep structures of the pelvic wall.

Stage VI. There is such extensive involvement of surrounding structures that not even the main tumor mass can be safely removed.

Crossen's classification is too long, but it distinguishes in an exceptionally lucid manner the various types of extrauterine extension.

Healy and Brown's<sup>13</sup> classification based on the size of the uterus consists of 4 groups:

Group I. Uterus normal in size, depth 3 inches.

Group II. Moderately enlarged uterus, depth  $4\frac{1}{2}$  inches, but not larger than a  $2\frac{1}{2}$  months' pregnancy.

Group III. Markedly enlarged uterus, 5 inches or more in depth, size of more than  $2\frac{1}{2}$  months' pregnancy.

Group IV. Extension of disease beyond the uterus.

Healy and Brown used an easily measured standard, the size of the uterus, but stress its value disproportionately and do not subdivide the extrauterine extensions of carcinoma.

Miller<sup>20</sup> similarly bases his classification on the size of the uterus as follows:

Group I. (Normal.) No palpable enlargement of the uterus, cavity measures 3 inches or less.

Group II. (Moderately enlarged.) Uterus enlarged to  $2\frac{1}{2}$  months' pregnancy, cavity measures less than  $4\frac{1}{2}$  inches.

Group III. (Markedly enlarged.) Uterus size of 3 months' pregnancy or more, cavity measures more than 5 inches.

This too depends on the size of the uterus which may be a fallible indicator. It also fails to classify extrauterine extension.

Scheffey, Thudium and Farell<sup>22</sup> divide endometrial carcinoma into: (1A) limited to the uterus, and (1B) spread beyond the uterus.

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## Original Communications

### A CLINICOPATHOLOGICAL CLASSIFICATION OF ENDOMETRIAL CARCINOMA BASED ON PHYSICAL FINDINGS, ANATOMICAL EXTENT, AND HISTOLOGICAL GRADE

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*(From the Department of Obstetrics and Gynecology of the Cornell University Medical College  
and the Woman's Clinic of the New York Hospital)*

THERE are many classifications of endometrial carcinoma, none of which has gained universal acceptance. Some divisions are based on clinical findings, others on gross pathological evidence, and still others on the microscopic appearance of the cancer. Despite the fact that panhysterectomy has been the generally preferred treatment for many years, a classification based on surgical and pathological findings has not been developed, standardized, and universally accepted. Cervical carcinoma, in sharp contrast, is divided into either one of two classifications: the League of Nations or the Schmitz. These divisions are universally accepted, even though they are based on clinical evidence alone and even though the specimens obtained by the current revival of surgery reveal errors in staging.

### Classifications of Endometrial Carcinoma

#### *Clinical Classifications.—*

The classifications of endometrial cancer have been based on clinical findings, gross pathology, or the microscopic picture. Some depend solely on one of these bases, while others have been combinations. Some of the prevalent clinical classifications are:

1. 1929 Heyman<sup>14</sup>
2. 1937 Crossen<sup>7</sup>
3. 1939 Healy and Brown<sup>13</sup>
4. 1940 Miller<sup>20</sup>
5. 1943 Scheffey, Thudium, and Farell<sup>22</sup>
6. 1947 Taylor and Becker<sup>26</sup>

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CASE 1.—Aged 39 years, white, gravida v, para iv. Curettage was performed 10 months previously, with a diagnosis of chronic endometritis. The cervix had a deep scar which extended into the left vaginal fornix. Contractions were irregular for 4 days after rupture of the membranes, and then became regular and strong. After ten hours the baby and placenta were delivered in bed; shock followed. The uterus and vagina were packed for moderate hemorrhage. Death in shock one-half hour later.

CASE 2.—Aged 31 years, white, gravida viii, para vii. Admitted to the hospital at 7 months for vaginal bleeding. Labor began one week later, and after 2 hours, a 4 pound, 8 ounce live fetus was precipitated in bed. Postpartum hemorrhage of about 750 c.c. occurred. Examination disclosed no tear. Treated by uterine packing, transfusion, and repacking. Death three hours after delivery. Autopsy showed a laceration on the left, just above the cervix; it was but 3 cm. long and 0.75 cm. deep, yet a large vessel had been torn. The serosa showed an extensive hemorrhagic area, but the tear was incomplete.

CASE 3.—Aged 28 years, white, gravida viii, para vii. After eleven hours of labor she complained of pain in the right side of the abdomen and flank. Contractions ceased and she became cold and clammy. Fetal parts could be clearly outlined and the abdomen was very tender. No external bleeding. X-ray showed breech presentation though a definite vertex presentation had been noted on admission; no definite outline could be seen about the fetus. Hysterectomy was performed 4 hours after rupture was suspected. The abdomen was full of blood and contained the placenta. The fetus was lying in a rupture in the left lower uterine segment. Death nine hours after operation.

CASE 4.—Aged 40 years, white, gravida xv, para xiv. Pendulous abdomen. Slight vaginal bleeding after 14 hours of labor, followed by shock, cessation of pains, and loss of fetal heart tones. Though a vertex presentation on admission, vaginal examination now showed a foot presenting and placental tissue in the vagina. A diagnosis of placenta ablatio was made. Autopsy showed a rupture of the uterus.

CASE 5.—Aged 32 years, Negro, gravida ix, para viii. Admitted in labor with membranes ruptured for three days. Contractions occurred every seven minutes, but after three hours the cervix remained undilated. Eight minutes later precipitate delivery was followed by profuse bleeding and shock. Examination disclosed a tear of the cervix extending into the left broad ligament and peritoneal cavity. Hysterectomy six hours after delivery. Death two hours later.

CASE 6.—Aged 43 years, Negro, gravida ix, para viii. After two hours of labor, the patient had a very strong uterine contraction that caused the uterus to stand out. This was followed by cessation of labor, slight vaginal bleeding, loss of the fetal heart tones, and shock. The fetus was palpated directly beneath the abdominal wall. Patient died two hours later. Autopsy showed about 3,500 c.c. of blood in the peritoneal cavity with the fetus and placenta free. There was a rent in the right lower segment.

CASE 7.—Aged 41 years, white, gravida vii, para vi. Pre-eclamptic toxemia. Admitted to the hospital after fifty-eight hours of ruptured membranes and ten hours of labor. Fetal parts could be palpated with unusual ease and the fetal heart sounds were not heard. There was tenderness in both flanks. At operation, the fetus and placenta were free in the peritoneal cavity and there was an irregular tear anteriorly in the lower uterine segment. Hysterectomy was performed and 2,000 c.c. of blood were transfused during the next twenty-four hours. Death three days later with anuria.

CASE 8.—Aged 39 years, white, gravida vii, para vi. One eclamptic convulsion was followed by regular uterine contractions; nine hours later, labor ceased and shock followed. Forceps delivery failed. Examination revealed a rent in the posterior wall of the uterus. A second convulsion was followed by death. Autopsy showed a rent in the posterior wall of the lower segment of the uterus through which the fetal head and an arm protruded.



Posterior pituitary extract should not be administered to the grand multipara, or to any multipara if a dense cervical scar is thought to be present. Nor should it even be given in premature labor or if there is mechanical hindrance to delivery, like hydrocephalus or transverse presentation. Whenever administered, the dose should not exceed one-half minim, and one of us employs one-eighth minim, diluting the extract one minim to one c.c. of normal saline solution. The time interval between doses should not be less than thirty minutes.

*Obstructive Dystocia—Hydrocephalus.*—In three cases hydrocephalus was not recognized, causing obstructive dystocia followed by spontaneous rupture of the uterus and death.

CASE 13.—Aged 27 years, white, para ii. The cervix was fully dilated after ten hours of labor and there was little progress thereafter. One hour later, the pulse became rapid and feeble, and the blood pressure could not be obtained. Rupture of the uterus was not suspected. On vaginal examination a brow presentation was diagnosed. A stillborn hydrocephalic fetus was delivered by forceps with difficulty. Death one hour later.

CASE 14.—Aged 31 years, white, para iii. This patient had twelve hours of labor before the uterus ruptured. At laparotomy, a hydrocephalic fetus with spina bifida was found free in the peritoneal cavity. There was a rent in the lower segment and into the broad ligament. Subtotal hysterectomy was performed. Death four hours after operation was due to hemorrhage and shock.

CASE 15.—Aged 36 years, white, para v. Membranes ruptured one week prior to admission to the hospital. The fetus appeared large and there was no engagement of the vertex. Shock followed nine hours of active labor. At laparotomy, the body of the fetus was found free in the abdomen with a hydrocephalic head in the uterus. Hysterectomy was performed, and a transfusion given. Death from peritonitis on the fifth day.

*Rupture of a Uterine Scar.*—In four cases death was due to rupture of a scar in the upper uterine segment; in the seventh month of pregnancy in two cases, and in two cases at term. In three cases, cesarean section had been performed previously, and in one case myomectomy. In two cases in which the area of rupture was closed by suture, death was due to pulmonary complication, the result of general anesthesia in one case. In two cases, hemorrhage and shock caused death. Diagnosis was confirmed by autopsy or operation in three cases.

*Other Causes.*—In eight cases, rupture of the uterus was due to varied or unknown causes. Two patients had cervical scarring, two had numerous abortions and were elderly, and one had a markedly pendulous abdomen. A classic picture of spontaneous rupture including vaginal bleeding, disappearance of the fetal heart sounds, shock, a globular mass to the side of the fetus and fetal parts easily palpable beneath the abdominal wall was present in five patients. Diagnosis was confirmed in seven cases either at operation or autopsy. In five cases hysterectomy was performed. Death was due to hemorrhage and shock within twenty-four hours in five cases, peritonitis (one case) and pneumonia (two cases). A brief case report showing the role of cervical scarring follows:

CASE 16.—Aged 37 years, white, gravida iii, para ii. Her past history included a difficult forceps delivery with cervical laceration. She was admitted to the hospital near term for a slight painless and apparently causeless hemorrhage. Vaginal examination showed no placenta and the membranes were ruptured artificially. After sixteen hours of labor, she went into shock. The fetal heart tones disappeared, a globular mass was palpated in the

Spontaneous rupture of the uterus in the "grand multipara" is generally attributed to weakening of the uterus as a result of myometrial pathology. We believe cervical scarring to be an important and unappreciated factor. In Case 5, a cervix which was unchanged after three hours of labor suddenly yielded and permitted a precipitate delivery eight minutes later. The tear in the cervix was continuous with rupture of the lower uterine segment. Case 1 also had an extensive scar of the cervix. There are five other cases in this series which showed cervical scarring; in two, rupture was spontaneous, and, in 3, traumatic.

*Pituitary Extract.*—Four patients received posterior pituitary extract during the first stage of labor. It had also been administered to an occasional patient elsewhere in this series but in these four cases it appeared to be responsible for rupture of the uterus. Two of these patients had operative procedures prior to recognition of the rupture; in one case, clinical evidence of rupture was noted before interference.

CASE 9.—Aged 39 years, white, gravida vi, para iii, admitted at term with ruptured membranes. Mild irregular pains occurred for twenty-two hours. The fetal heart rate was normal, the cervix 3 cm. dilated and the vertex was at station minus 3. After six doses of 1 minim each of posterior pituitary extract at about 20-minute intervals, the patient became orthopneic and cyanotic. A diagnosis of rupture of the uterus was made and operation was performed one hour later. At operation, a rent was found in the posterior lower segment of the uterus extending into the right broad ligament with free and clotted blood in the right retroperitoneal space behind the cecum. Hysterectomy was performed and 3,000 c.c. of blood were given by transfusion. Death in shock two hours after operation.

CASE 10.—Aged 45 years, white, gravida iv, para iii, admitted to the hospital at term. A breech presentation was diagnosed. After twenty hours of labor the cervix was fully dilated, and contractions became weak and irregular. Two 5-minim doses of posterior pituitary extract within one-half hour increased the intensity of the contractions; 11 minims were given fifteen minutes after the second dose. Shock followed immediately. Vaginal examination showed a transverse presentation, and rupture of the uterus was diagnosed. At operation, the abdomen contained a large amount of blood and the placenta. A rent in the posterior surface of the uterus extended from the cervix to the fundus with a large hematoma beneath the bladder. The fetus was free in the peritoneal cavity with the hydrocephalic head and an arm still contained in the uterus. Hysterectomy was performed rapidly. Death from peritonitis on the fourth postoperative day.

CASE 11.—Aged 30 years, gravida iv, para iii, admitted to the hospital at term with weak and irregular pains. The umbilical cord and an arm prolapsed. They were repositioned and the vertex pushed over the pelvic inlet. Following two 1-minim doses of posterior pituitary extract, contractions became strong and were followed by spurts of vaginal bleeding. The patient became pale and the pulse rapid. When a second examination revealed recurrence of transverse presentation, internal version was performed. She was treated for shock and improved. No contractions occurred despite twelve more doses of pituitary extract. She died of peritonitis on the fourth day, undelivered. Autopsy showed the abdomen to contain 3,000 c.c. of blood and the fetus. There was a rent in the lower segment through which the placenta protruded.

CASE 12.—Aged 33 years, white, gravida iv, para iii, admitted to the hospital in active labor. About 16 hours later "5 units" of posterior pituitary extract were given and an unsuccessful attempt at forceps delivery was followed by shock. At operation eight hours later, a large amount of blood and the fetus were found in the abdominal cavity. There was a tear 6 inches long in the right lower segment. Hysterectomy was performed with transfusion of 3,000 c.c. of blood. Death was due to hemorrhage and shock.

*Ovarian tumor:*

CASE 18.—Aged 28 years, white, gravida ii, para i. After fifty-eight hours of labor and although the cervix was not fully dilated, a difficult internal version and extraction were performed. Hemorrhage and shock followed. Examination showed a tear in the lower uterine segment anteriorly, extending from one broad ligament to the other. A mass which proved to be a dermoid cyst of the ovary was felt. After uterine packing and transfusion, hysterectomy and oophorectomy were performed. Death on the following day of hemorrhage and shock.

*Forceps.*—Nine patients had forceps application followed by attempts at, or actual, forceps delivery which resulted in rupture of the uterus. In the etiological factors noted were two cases of cervical scarring, one case of placenta previa, and three persistent occipital posterior positions. Two patients died undelivered because of failed forceps. Three had forceps rotation, one by the Scanzoni maneuver. In the placenta previa case, a cervix dilated only 3 cm. was incised laterally before forceps extraction. Severe shock with but moderate vaginal bleeding was noted in nearly every case. The diagnosis was proved in six cases. Two patients were treated by packing and one by hysterectomy. Eight patients died of hemorrhage and shock within nine hours, and seven within three hours. One patient died of peritonitis eight days after delivery.

*Craniotomy.*—Three patients died following craniotomy. In two cases, forceps extraction had failed. Diagnosis was confirmed at autopsy in two patients who died of hemorrhage and shock within one hour after delivery.

*Fundal Pressure.*—In three cases, rupture of the uterus was the result of strong fundal pressure. In two there was impaction of the shoulders of fetuses weighing  $11\frac{1}{2}$  and 14 pounds. All ruptures were proved. Death was due to anesthesia for hysterectomy (one case), hemorrhage and shock (one case), and peritonitis (one case). A case report follows:

CASE 19.—Aged 41 years, gravida iii, para ii. Delivery was attempted at home by strong fundal pressure after full dilatation of the cervix. Slight vaginal bleeding, rapidity of the pulse, and sudden cessation of pains followed. On admission to the hospital, there was considerable distention of the abdomen with a large globular mass on the right and another mass in the left lower quadrant of the abdomen. The caput was showing, fetal heart tones were absent, and the patient was vomiting. A diagnosis of rupture of the uterus was made. At operation the abdomen was full of blood due to rupture of the left lower segment of the uterus with tearing away of the broad ligament. While the fetus was delivered from below, hysterectomy was performed. Vomiting and aspiration during general anesthesia caused death.

*Pinard Maneuver and Bagging.*—

One patient had a Pinard maneuver for a breech presentation complicated by placenta previa. A 9 pound, stillborn infant was partially extracted. Hysterectomy was performed for rupture of the uterus, with death from hemorrhage and shock on the operating table. The second patient had many complications including toxemia of pregnancy, jaundice, premature separation of the placenta, and intrapartum infection. Treatment consisted of bagging, administration of posterior pituitary extract, and forceps delivery. Incomplete rupture of the uterus caused hemorrhage and shock. Death on the day of delivery.

**Diagnosis**

When the uterus ruptures during labor, its recognition should be easy, yet diagnosis is often missed or unduly delayed, partly because rupture occurs but rarely in the experience of any individual, and perhaps because the

right side of the abdomen, and the fetal parts were easily palpable on the left. At operation, the fetus, placenta, and about 500 c.c. of blood were found free in the peritoneal cavity. The rupture in the lower segment involved the entire cervix, extending to the middle of the corpus. Death occurred during hysterectomy.

### Traumatic Rupture

*Version.*—This procedure is the most common cause for rupture of the uterus, accounting for twenty deaths in this series. The secondary etiological factors in this group were transverse presentation, placenta previa, failed forceps, and ovarian tumor. Cases will be discussed under these subdivisions.

*Transverse presentation:* In eight cases transverse presentation was treated by internal version; extraction was prompt in every case but one. All were multiparas; five had ruptured membranes for more than thirty hours, and three of these were in labor for thirty-six hours or more. In many cases, although the cervix was not fully dilated at the time of version, extraction was performed. It is noteworthy that, although some reports described the ease with which internal version and extraction had been done, rupture of the uterus nevertheless resulted. The clinical picture of vaginal bleeding and shock out of proportion to the blood loss was constant, yet hysterectomy was performed in but two cases. Diagnosis was confirmed at operation or examination after death in five patients. One patient died of peritonitis on the third day, while the others died of hemorrhage and shock within twenty-four hours after rupture, four within three hours, indicating the speed with which uterine rupture can cause death. An illustration of this type of case follows:

Case 17.—Aged 32 years, white, gravida ii, para i, admitted near term and in labor. The presentation and position of the fetus were not definitely determined. After forty hours of labor with membranes ruptured for thirty-one hours a fetal arm was noted protruding through the vulva. Under ether anesthesia, internal version and extraction of a 6 pound, macerated fetus were performed. Shock, with but slight vaginal bleeding, followed this procedure. It was felt inadvisable to operate because of her poor general condition, and small amounts of blood were transfused. Death occurred twenty-four hours after delivery. Autopsy showed intraperitoneal hemorrhage and a ragged tear in the left lower uterine segment.

*Placenta previa:* In six cases, placenta previa had been treated by internal version and extraction. In no case was there evidence that the cervix was fully dilated before extraction, and, in fact, in one case the type of version was Braxton Hicks. All patients died of hemorrhage and shock, five within a few hours of delivery. It is well accepted that when Braxton Hicks or internal version is performed for placenta previa, it is hazardous to attempt extraction because of the friability of the lower uterine segment. As a matter of fact, since studying 50 deaths from placenta previa in Brooklyn,<sup>2</sup> we are convinced that in treatment of placenta previa, Braxton Hicks and other forms of version should be abandoned.

*Failed forceps:* In five cases, rupture of the uterus was due to internal version and extraction performed after attempts at forceps delivery had failed. In four cases, 34 to 52 hours of labor preceded the delivery. A retraction ring was present, and the cervix incompletely dilated in three cases. Forceps application was high in four cases. Diagnosis was proved in four cases, one by examination and three at autopsy. In two of the latter, exploration of the uterus before death had failed to reveal the rupture. Death was due to peritonitis in three cases and to shock in two cases.

tion may consist only of rapid excision of the uterus between broad ligament clamps and abdominal closure with through and through interrupted sutures; the clamps may be removed on the third day.

In the event of rupture of the uterus with the presenting part low in the birth canal, extraction of the fetus is definitely contraindicated. Though vaginal delivery may in rare cases save the fetus, it enlarges the tear, increases hemorrhage, wastes valuable time, and markedly lessens the patient's chance for recovery.

If rupture of the lower uterine segment is minimal and known to be incomplete and hemorrhage into the broad ligament and parametrium is not great, rupture may be repaired from below. If there is any doubt about complete control of hemorrhage, the abdomen should be opened at once. Tamponade may at times be satisfactory, but it is not advised.

In almost every case, transfusion spells the difference between life and death. As a rule, less than 1,000 c.c. is futile, and it may be that 3,000 c.c. or more of blood will be required. If, as is advised, 1,000 c.c. of compatible blood are available on every delivery floor, this will tide the patient over until more is obtained. It may be wise to make use of more than one venous portal for transfusion. Femoral veins are practical avenues for transfusion of blood and much better than time-consuming and often futile cutdown upon collapsed veins elsewhere.

### Summary

1. The clinical data of sixty-four deaths from rupture of the uterus are presented; twenty-seven were spontaneous and thirty-seven were the result of trauma.

2. In all but three cases, rupture took place in the lower segment of the uterus. The role of cervical scarring in the etiology of rupture is emphasized.

3. Internal version is the most frequent cause and should be recognized as an extremely hazardous procedure under certain unfavorable conditions.

4. That strong fundal pressure can rupture a uterus is shown by three cases in this series.

5. Four deaths occurred from the use of pituitary extract during the first stage of labor. Despite this, the judicious use of minute doses in carefully selected cases of uterine inertia is advised.

6. The diagnosis of rupture of the uterus is often not made sufficiently early for survival of the patient. Routine exploration of the uterus after traumatic vaginal procedures is indicated, especially if shock is present.

7. The essence of adequate treatment for complete rupture of the uterus is prompt massive blood transfusion and hysterectomy. Shock is no contraindication to operation.

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obstetrician fears that he may open the abdomen in error. Procrastination is in fact the most important cause of death. Except in the case of the grand multipara, threat or imminence of rupture should be recognized.

In persistent brow, face, and scapular presentations, spontaneous delivery can occur only under unusual circumstances. When there is an obstacle to delivery, whether it be a pelvic tumor or hydrocephalus, when the cervix is fully dilated and the vertex remains unengaged in spite of increasing frequency and intensity of uterine contractions, and when the lower segment is thinly stretched up to a pathological retraction ring, rupture of the uterus threatens. The appearance and behavior of the patient will point to the gravity of the situation.

At that time, sudden and complete relief of the pain of labor with cessation of uterine contractions is evidence of uterine rupture. Vaginal bleeding is significant, though not often sufficiently great to account for deepening anemia and shock. Vaginal examination and abdominal palpation may show recession of the presenting part or actual change of pole, and the fetus itself may be easily felt outside a hard contracted uterus. However, the fetus may not escape from the uterus or may be fixed deep in the birth canal, and, in fact, may be delivered alive. Fetal heart tones may not be lost at once and symptoms of intraperitoneal hemorrhage may be delayed for several hours.

When rupture of the uterus is the result of trauma incident to internal version, with or without breech extraction, forceps delivery or craniotomy, diagnosis is most often missed. Not because diagnosis is difficult to make, but it is assumed that hemorrhage and shock are due to trauma and anesthesia, and not to rupture.

When hemorrhage and shock follow a major vaginal operative procedure, the uterus should be explored. Exploration is indicated after internal version and after any delivery in which shock appears to be an inconsistent sequel. The danger incident to examination of the uterine cavity is far less than the risk of delay or failure of diagnosis. If rupture of the lateral uterine wall is not found, the anterior and posterior walls should be examined with special care.

### Management

Impending rupture of the uterus demands immediate treatment. Tetanic contractions of the uterus may be fairly controlled by administration of ether or chloroform during preparation for delivery. If vaginal delivery is practicable, any operative procedure must be performed with utmost gentleness and care. Internal version is absolutely contraindicated. No attempt should be made to dislodge the presenting part or to thrust the fetus upwards as these procedures will probably result in rupture of the excessively thinned-out lower segment. If forceps are applied to the vertex, the blades must be introduced carefully, and if slight trial traction fails to bring about advance no further test may be made. At times, perforation of the head is preferable. If cesarean section is elected, hysterectomy may be necessary.

As a rule, complete rupture of the uterus will result in death unless adequate treatment be instituted within a few hours. The cardinal principles of good treatment are massive transfusion and immediate operation. When rupture has occurred through a previous cesarean section scar, excision of the old scar and resuture, if feasible, is preferred. If the uterine laceration is irregular and raggid, then supravaginal hysterectomy will be necessary. The operation should be performed with speed and gentleness with little attention to refinements of technique. In apparently hopeless cases, opera-



Table I shows that 27 cases of chorionepithelioma developed in women who had from one to not more than five pregnancies, three of which resulted in full-term babies, whereas 43 out of 70 cases of chorionepithelioma developed in women who were gravida vi, para iv to gravida xix, para xiv. The same table also shows that ten cases, or in 14.28 per cent of all the pregnancies of the women affected, did not reach beyond three months. The table further shows that only three out of 70 women had neither abortion nor hydatidiform mole.

One question to which we wanted to find the answer was whether there was correlation in the age incidence of parturition, abortion, hydatidiform mole, and chorionepithelioma; hence the formation of Table II which shows that the greatest age incidence of parturition, 59.35 per cent, is in the third decade, between the ages of 20 and 29 years. The same is true with hydatidiform mole, though the percentage is lower, 44.52 per cent. But the greatest age incidence of abortion, 54.71 per cent, is in the fourth decade, 30 to 39 years. The same is true with chorionepithelioma, though the percentage is lower, 39.06 per cent. In the fifth decade, 40 to 46 years, the percentage incidence of parturition was only 3.72; abortion, higher than parturition, 11.32 per cent; hydatidiform mole, higher than abortion, 13.86 per cent; and chorionepithelioma, higher than mole, 18.74 per cent. From 50 to 52 years, there were no cases of parturition nor of abortion but there were one case (0.72 per cent) of hydatidiform mole and two cases (3.12 per cent) of chorionepithelioma.

TABLE II. RELATIVE INCIDENCE OF PARTURITION, ABORTION, HYDATIDIFORM MOLE, AND CHORIONEPITHELIOMA ACCORDING TO AGE

AGE (YEARS)	APRIL 5, 1945 TO APRIL 5, 1946				JAN. 1, 1940 TO DEC. 31, 1943		DEC. 16, 1941 TO DEC. 31, 1946	
	PARTURITION		ABORTION		HYDATIDIFORM MOLE		CHORIONEPITHE- LIOMA	
	NO. OF CASES	PER- CENTAGE	NO. OF CASES	PER- CENTAGE	NO. OF CASES	PER- CENTAGE	NO. OF CASES	PER- CENTAGE
15 to 19	34	6.06	7	6.60	23	16.71	6	9.37
20 to 29	333	59.35	29	27.35	61	44.52	19	29.69
30 to 39	173	30.83	58	54.71	33	24.08	25	39.06
40 to 46	21	3.72	12	11.32	19	13.86	12	18.74
50 to 52	0	0			1	0.72	2	3.12
Unknown age							6	

Table II, then, shows that the optimum age for pregnancies to reach full-term is between 20 and 29 years. However, hydatidiform mole has also its greatest incidence during this age period. The fourth decade (30 to 39 years) has the peak incidence of both abortion and chorionepithelioma, exceeding that of parturition. And after the age of 40, the percentage incidence of abortion, mole, and chorionepithelioma far exceeds that of parturition. It is interesting to note also that before the age of 20 years the percentage incidence of abortion, mole and chorionepithelioma slightly exceeds that of parturition.

All concede that over 50 per cent of chorionepitheliomas develop from hydatidiform mole.

Table III demonstrates that the type of pregnancy giving rise to chorionepithelioma in two different series studied, namely, 70 cases from Dec. 16, 1941, to Dec. 31, 1946, and an earlier study of 72 cases<sup>2</sup> up to Dec. 15, 1941, give about the same percentage. Hydatidiform mole was the antecedent of chorionepithelioma in 62.85 per cent and 62.5 per cent, respectively; abortion in 24.28 per cent and 23.61 per cent, respectively; labor in 10 per cent and 11 per cent, respectively.

# STATISTICAL STUDY OF CHORIONEPITHELIOMA IN THE PHILIPPINE GENERAL HOSPITAL

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THIS is a continuation of the studies on chorionepithelioma begun since Acosta-Sison et al.<sup>1</sup> published the first 6 cases that recovered. Interest in the subject started only in 1936, and up to Dec. 15, 1941, we have gathered for study 72 cases.<sup>2</sup> From Dec. 16, 1941, to Dec. 31, 1946, we have admitted to the Philippine General Hospital 70 cases, making a total of 142 cases. Only one case was seen in the last two weeks of 1941, so that 69 cases were admitted in five years (1942-1946), giving an average of over thirteen cases per year. We admit that this incidence is very high when compared to that of London Hospital as presented by Brew,<sup>3</sup> who found only 24 cases in 52 years (1885 to 1937) an average of one case every two years. We have no explanation for this, just as we cannot explain why we have a very high incidence of hydatidiform mole. Acosta-Sison et al.<sup>4</sup> gave an incidence of hydatidiform mole in the Philippine General Hospital of one for every 126 pregnancies, in contradistinction to Mathieu's<sup>5</sup> figure which is one for every 2,000 pregnancies. All we can say is that though both conditions are found in primigravidas they are more common in multigravidas and multiparas, and Filipino women are very prolific, having as many as 19 pregnancies. It seems that the frequent subjection of the individual to pregnancy, especially if the pregnancies rapidly succeed one another, but more especially if they terminate in the early months as abortion or mole, favors the development of chorionepithelioma. To this we have to add that Philippine General Hospital is what may be called the wastebasket of pathologic cases, especially obstetrical ones.

TABLE I. INCIDENCE OF CHORIONEPITHELIOMA ACCORDING TO GRAVIDITY AND PARITY 70 CASES\*

NO. OF CASES		
Gravida i to gravida ii	10	} 27 cases
Gravida i, para i	2	
Gravida ii, para i	8	
Gravida ii, para ii	1	
Gravida iii, para ii to gravida v, para iii	6	
Gravida vi, para iv	9	} 43 cases
Gravida vi, para v to gravida ix, para vii	16	
Gravida ix, para viii to gravida x, para ix	7	
Gravida xii, para ix to gravida xvii, para xi	5	
Gravida xiv, para xiii to gravida xix, para xiv	6	

\*Of the 70 cases, only three had had neither abortion nor hydatidiform mole. In ten cases, or in 14.28 per cent, the pregnancies did not reach beyond three months. Only ten patients, or 14.28 per cent, were primiparas; the rest were multigravidas and multiparas.

We have employed with success the HBEs method as introduced by Acosta-Sison.<sup>11</sup> The method is nothing but the careful interpretation of the combined history, symptomatology, and physical findings. Since all our cases gave a history of having expelled the product of conception, from a few days, weeks, or months, to as long as three or more years before, and had complained of abnormal uterine bleeding, and on bimanual examination showed enlargement and softening of the uterus, the method was labelled as HBEs for short. Histology and the laboratory animal for hormonal determination were also used at times. The former was used always for confirmation of the diagnosis after hysterectomy or at autopsy.

We routinely send the pathologist the last curettings of every case of hydatidiform mole and of incomplete abortion for detection of malignancy. For this method, we employed the term "early microscopy" to distinguish it from what is ordinarily called diagnostic curettage or the curettage done for the purpose of determining the cause of any uterine bleeding occurring sometime after the expulsion of the product of conception.

The Aschheim-Zondek or Friedman test was used in combination with the other methods of diagnosis or in the follow-up of cases operated upon, wherein it is most valuable.

TABLE IV. METHOD OF DIAGNOSIS IN 70 CASES

	NO. OF CASES
HBEs positive and used as basis of diagnosis	43
3 of these were reported as malignant by early microscopy but operation was postponed until 1 month after the dilatation and curettage because of youth of the patients.	
1 was reported as benign by early microscopy.	
1 was reported as negative for chorionepithelioma by diagnostic curettage.	
All these 43 cases showed chorionepithelioma grossly and microscopically in the hysterectomized uterus.	
HBEs positive but preoperative diagnosis by another physician was uterine myoma	1
HBEs positive and the chorionepithelioma was confirmed at autopsy; not operated upon	1
HBEs positive but the positive diagnosis by diagnostic curettage was the basis of diagnosis	8
HBEs positive but preoperative diagnosis was ruptured tubal pregnancy	3
HBEs positive but preoperative diagnosis was cancer of the corpus uteri. Correct diagnosis was established only after biopsy of the hysterectomized uterus	2
Diagnosed as malignant mole because of marked discrepancy in the enlargement of the uterus as related to the length of amenorrhea	1
Hysterectomy was done with the mole in situ. Biopsy showed malignant mole.	
By early microscopy	11

Table IV shows that 43 cases have been diagnosed by HBEs. Three of these had been previously reported as malignant by early microscopy but because of the youth of the patients the operation was withheld, hoping the pathologist committed an error. But at the end of five weeks, HBEs was present, so the three patients were finally hysterectomized, although one was reported as benign mole by early microscopy, and one was reported negative for malignancy by diagnostic curettage. All the 43 cases showed chorionepithelioma grossly and microscopically in the hysterectomized uterus. In sixteen cases, HBEs was present but was not used as basis of diagnosis. The diagnosis in one case was uterine myoma; in three cases, ruptured tubal pregnancy; in two cases, cancer of corpus uteri. The correct diagnosis was made only at biopsy of the hysterectomized uterus. In eight cases, diagnostic curettage was used as the basis of

TABLE III. TYPE OF PREGNANCY GIVING RISE TO 70 CASES OF CHORIONEPITHELIOMA  
FROM DEC. 16, 1941, TO DEC. 31, 1946

	NO. OF CASES	PERCENTAGE	PERCENTAGE INCIDENCE OF PREVIOUSLY REPORTED 72 CASES UP TO DEC. 15, 1941
Hydatidiform mole	44	62.85+	62.5
Abortion	17	24.28+	23.61
Twins			
a. Mole			
b. 4 month fetus and normal placenta	1	1.42	
Miscarriage	1	1.42	
Premature labor 2}			
Full-term labor 5}	7	10.00	11

In a study of 136 cases of mole, Acosta-Sison et al.<sup>4</sup> have found that 30 cases, or 22.05 per cent, became malignant. This is a much higher percentage than the 5 to 16 per cent of malignancy from hydatidiform mole as given independently by Sunde and Findley who were cited by Stander.<sup>6</sup> It is not surprising that hydatidiform mole is the most common source of chorionepithelioma for the main pathology of hydatidiform mole is not so much the cystic degeneration of its mesodermic core, though this exists, as the undue proliferation of its epithelial elements, the Langhans' and syncytial cells, which, because of their excessive hormone formation, render the uterus with its enlarged vessels easily susceptible to their invasion and growth. In abortion, from which arises over one-fifth of the cases of chorionepithelioma, the epithelial elements of the chorionic villi are also quite active, in contradistinction to their condition toward full term, when senility of the placenta begins to make headway. Moreover, after the fifth month, the Langhans' cells not being needed any more become hyalinized and disappear. It may be that in the few cases of chorionepithelioma that develop after full term the Langhans' cells have persisted so that eventually they become abnormally active.

The method of diagnosis as given in the literature is the presence of chorionepithelioma cells in the diagnostic curettage or in the positive Aschheim-Zondek or Friedman test after the expulsion of the product of conception. When either or both of these tests are positive, they are of great help in arriving at a diagnosis. But we had at least two cases which consistently gave a negative diagnostic curettage on more than one occasion and in which the true nature of the disease was not discovered until laparotomy was made because of internal hemorrhage which was thought to be due to ruptured tubal pregnancy.

With regard to Aschheim-Zondek or Friedman Test, our experience is that they are, often negative in cases of early chorionepithelioma. We had one case that had a negative Friedman test four months after an abortion from which the chorionepithelioma developed. Schuman,<sup>8</sup> in discussing McLaughlin's paper on mole followed by chorionepithelioma, cites his own case where the Aschheim-Zondek test was negative for one year. The test became positive only one month before the patient died. Chesley et al.,<sup>9</sup> in their studies on hydatidiform mole, report a case that developed chorionepithelioma in which the Friedman test was negative on the twenty-second day after the expulsion of the mole. On the other hand, they had cases of benign mole that did not develop chorionepithelioma in which the Friedman test was positive as long as over seven months after the expulsion of the mole. Hamburger<sup>10</sup> also reports that, in a follow-up study of 72 cases of hydatidiform mole, 9 per cent gave positive Friedman tests three months after the evacuation of the uterus, in spite of the fact that they did not develop chorionepithelioma.

*Site of the Primary Growth.*—As is to be expected, the endometrium was the part most frequently involved. Table VI shows that it was the site of primary growth in 58 cases, or 82.85 per cent. This is fortunate in the sense that when the endometrium is the primary site of the growth, uterine bleeding comes earlier and this may lead the patient to consult the physician earlier and such a growth is one amenable to the correct diagnosis by a diagnostic curettage. In twelve cases, the myometrium was the primary site. In five of these cases, there was extension of the growth into the endometrium. But, in eight cases, the endometrium was free from the growth so that a diagnostic curettage would render a negative finding of the growth. This was the result in those cases so operated upon, giving the physician and the patient a sense of false security. Seven of the myometrial cases died. In four of them, the uterus was perforated so that there was much hemoperitoneum causing the fatality.

TABLE VII. SITES OF METASTASIS

Lungs	7 cases
Lungs and brain	4 cases
Parametrium	3 cases
Vagina and parametrium	2 cases
Vagina	3 cases
Broad ligaments	4 cases

*Sites of Metastasis.*—As in a previous study made of 72 cases,<sup>1</sup> the lungs, vagina, and brain were found to be the most frequent sites of metastasis.

Table VII shows that among 70 patients there was metastasis in the lungs in eleven cases, in four of which there was also a concomitant metastasis in the brain. The parametrium was involved in five cases, in two of which the metastasis had extended into the vagina. Metastasis into the broad ligaments was found in four cases.

The metastasis into the lungs, brain, and the lower vaginal canal is carried by the blood stream, whereas the affection of the broad ligaments, parametrium, and upper part of the vagina must have taken place by the extension of the growth into these regions.

TABLE VIII. CONDITION OF THE OVARIES AS FOUND ON LAPAROTOMY OF 64 CASES

In 38 cases, 59.37 per cent, the ovaries were either cystic or were converted into ovarian cysts.
In 1 case, both ovarian cysts were the size of a grapefruit.
In 8 cases, both ovarian cysts were the size of an orange.
In 10 cases, both ovaries were cystic.
In 11 cases, only the right ovary was cystic.
In 8 cases, only the left ovary was cystic.

The ovaries, as shown in Table VIII, were found either to be cystic or to have been converted into cysts in 38 cases, or 59.37 per cent, of the 64 patients laparotomized. In eight cases, both ovaries had been converted into ovarian cysts having the size of an orange. In one case, both ovarian cysts were as large as a grapefruit. It is said that the cystic condition of the ovaries or their conversion into ovarian cysts is due to their abnormal hormonal stimulation from the chorionic cells of either the hydatidiform mole or chorionepithelioma and that the eradication of either brings about their recession. However, we saw at least three cases of hydatidiform mole where the concomitant ovarian cysts not only did not disappear but grew much bigger and these cases of hydatidiform mole did not develop chorionepithelioma.

diagnosis. In one case, the hydatidiform mole was diagnosed as malignant because of the marked discrepancy between the size of the uterus (7 months) and the length of amenorrhea (2 months) and hysterectomy was done with the mole in situ. Biopsy showed malignant mole. Early microscopy was the basis of diagnosis in eleven cases. The hysterectomized uteri of all these patients showed foci of chorionepithelioma.

In the Philippines, where chorionepithelioma is not infrequent and where many lives on its account have been lost, one cannot emphasize the necessity of early radical treatment before metastasis occurs. And this necessarily involves early diagnosis. The steps we have taken to attain this are to examine histologically the last curettings of every case of mole or incomplete abortion for malignancy; then every patient curetted for mole is instructed to return to the hospital any time she has abnormal bleeding or, in its absence, after four to six weeks, when HBEs method may be applied.

TABLE V. MANAGEMENT OF 70 CASES OF CHORIONEPITHELIOMA

	NO. OF CASES
Hysterectomy (total or subtotal)	64
In 38 cases unilateral or bilateral salpingo-oophorectomy was also performed because of the involvement of the ovaries.	
In 4 cases the uterus was perforated and there was hemoperitoneum.	
In 1 case hysterectomy was done with the mole in situ. Histopathology showed malignant mole.	
In 4 cases the hysterectomy was followed by x-ray. 1 of these, in spite of complete hysterectomy followed by x-ray, developed vaginal metastasis from which the patient died.	
Not operated upon because of advanced metastasis in brain and lungs, confirmed by autopsy	4
Not operated upon because of advanced vaginal metastatic growth. X-ray and radium treatment proved futile. (Died of hemorrhage from vaginal growth)	1
Refused operation and eventually died at home	1

Table V shows that hysterectomy, total or subtotal, was performed in 64 cases. This was accompanied by unilateral or bilateral salpingo-oophorectomy in 38 cases where one or both ovaries had been affected. In 4 of the hysterectomized cases the uterus was found to be perforated by the growth and there was much hemoperitoneum. In one case, hysterectomy was done with the mole in situ. Histology of the uterus showed malignant mole. In four cases, the hysterectomy was followed by x-ray treatment because of incomplete removal of the chorionepithelioma cells at the broad ligament. One of these cases, in spite of complete hysterectomy followed by deep x-ray treatment, developed extensive vaginal metastasis from which the patient died. Four cases were not operated upon because of advanced metastasis in the lungs and brain, confirmed at autopsy. One case was also not operated upon because of advanced parametrial and vaginal metastasis when the patient was first seen. X-ray and radium treatment in this case proved futile. The patient died of hemorrhage from the vaginal growth. One woman refused operation and x-ray treatment and she eventually died at home.

TABLE VI. SITE OF PRIMARY GROWTH

Endometrium with extension to myometrium	58 cases
Myometrium with extension to endometrium	5 cases
Myometrium alone	8 cases
7 of these patients died. In 4 of those that died, there was uterine perforation with hemoperitoneum.	

### Summary

An analysis of 70 cases of chorionepithelioma admitted from Dec. 16, 1941, to Dec. 31, 1946, is presented. In addition to the 72 cases previously reported, this makes a total of 142 cases.

Tables of the most frequent age incidence, type of pregnancy that gives rise to chorionepithelioma, the sites of primary growth, the sites of metastasis, methods of early diagnosis, condition of the ovaries, and causes of mortality are discussed.

Attention is called to the limitation and even danger of diagnostic curettage in certain cases as a means of diagnosis. Its verdict when positive may be true but when negative does not necessarily mean absence of malignancy. The HBEs method should then be used, supplemented, if desired, by hormonal determination.

Early microscopy and the follow-up of every case curetted for hydatidiform mole will help to detect the early cases.

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TABLE IX. MORTALITY

OF THE 70 PATIENTS, 17, OR 28.57 PER CENT, EITHER DIED OR WENT HOME IN SERIOUS CONDITION	
CAUSE OF DEATH	NO. OF CASES
Hemorrhage after curettage (no donor)	1
Hepatitis and pyelonephritis after healed wound from hysterectomy. Patient was transfused with blood from a donor who had a history of malaria	1
Sudden death after healing of abdominal wound. Death unexplained by autopsy	1
Perforation of uterus by the growth with much hemoperitoneum; 1 of these was complicated by peritonitis	4
Peritonitis due to concomitant double pyosalpinx	1
Metastasis, broad ligament and lungs. Lung metastasis looked like miliary tuberculosis. Died soon after diagnostic curettage (not laparotomized)	1
Metastasis, lungs and brain (3 of these were not operated upon)	4
Metastasis, parametrium and vagina, extensive. (1 developed metastasis after panhysterectomy followed by x-ray)	2
Metastasis, lungs, extensive (not operated upon)	2

Table IX shows that the mortality of the 70 cases was 17, or 28.57 per cent. Nine deaths were due to extensive metastases. One death was caused by hemorrhage after dilatation and curettage for what was supposed to be incomplete abortion but which on biopsy turned out to be chorionepithelioma. No donor was then available. Nine of the 17 patients were hysterectomized. One of these patients died of hepatitis and pyelonephritis (autopsy findings) after blood transfusion from a donor who gave a history of malaria. The abdominal wound of this case healed by first intention. One patient died suddenly after the healing of the abdominal wound by first intention. Death in this case could not be explained by autopsy. Three patients died of intra-abdominal hemorrhage because of perforation of the uterine wall by the growth. One patient died of peritonitis because of concomitant bilateral pyosalpinx. The uterus of this case was also perforated. One patient died a few days after the diagnostic curettage. Autopsy showed extensive chorionepithelioma in the uterus, metastasis in both broad ligaments, and diffuse metastasis in the lungs looking like miliary tuberculosis. Microscopic examination of the lungs showed diffuse infiltration of Langhans' and syncytial cells. I believe that the miliary tubercular-looking metastasis in the lungs of this patient was provoked by the diagnostic curettage. HBEs was clearly present and diagnostic curettage should not have been employed. This case was not laparotomized.

The main causes of death were the extensive metastases and hemorrhage from the growth. However, early extirpation of metastasis in the lower part of the vagina, if localized, results in cure. The same may be said with the early metastasis in the lungs when promptly treated by x-ray. We cannot say the same with regard to the metastasis in the brain, for the four cases of brain metastasis in conjunction with metastasis in the lungs in this study of 70 cases, and the ten cases of brain metastasis in a previous study of 72 patients were all fatal.

The only hope for cure of chorionepithelioma is its early recognition and complete eradication before metastasis occurs.

Assertion had been made that extirpation of the primary growth, say in the uterus, brings about the recession of metastasis in other parts of the body. This claim has not been substantiated in our cases. The foci of chorionepithelioma, wherever they may be, and be they primary or metastatic, should always be completely eradicated surgically, if accessible, and by x-ray, if inaccessible to the knife. And this must be done early if the patient is to survive.



At operation, the uterus was opened by a classical incision and a gush of grapelike clusters of hydatidiform mole escaped through the incision. The uterus was completely evacuated, and the endometrial cavity was wiped clean with laparotomy pads. There was no evidence of invasion of the uterine wall. No fetus or placenta could be demonstrated.

Pathologic study of the specimen was reported as typical of hydatidiform mole, both grossly and microscopically.

The patient responded well to the usual postoperative measures, and her convalescence seemed relatively uneventful. On the first postoperative day, the hemoglobin was found to be 13 per cent or 2.2 Gm. Replacement therapy of whole blood by transfusion was continued. The blood pressure remained at 140/90.

On March 26, the hemoglobin was 74 per cent or 11.4 Gm. The carbon dioxide combining power was 54 per cent. Blood urea nitrogen was 13 mg. per cent, and the blood chlorides were 480.

On March 28, during her morning bath, the patient was suddenly seized by a generalized convulsion which lasted five minutes. A second convulsion lasting three minutes occurred at 6:25 A.M., one-half hour later; and a third and final convulsion, three minutes in length, began at 7:10 A.M. There was no cry, no incontinence of urine or feces, and, as determined later from the patient, no preceding aura. The blood pressure was 162/104 at 8:30 A.M. and had risen to 174/120 by 10:45 A.M. There was a 3 plus albuminuria. The carbon dioxide combining power was determined to be 42 per cent, while the uric acid level was 4.2.

The patient remained semicomatose and disoriented throughout the next forty-eight hours, morphine being given only to control excessive restlessness.

Visualization of the eye grounds revealed no papilledema or hemorrhages, but some edema and exudate were noted, and the vessel ratio was reduced 1:3.

The Hanger cephalin flocculation test on March 30 was reported as 2 plus after 24 hours, 3 plus after 48 hours, thus indicating some liver damage.

The patient continued to improve rapidly thereafter. On April 1, the blood pressure was 140/90 and there was no albuminuria. The vulvar edema and that of the thighs had subsided. The patient was allowed out of bed on April 3. Her progress continued to be favorable, and she was discharged on April 12.

At the time of her discharge, her blood pressure was 124/76. The Hanger cephalin flocculation test was reported as equivocal after 24 hours, 1 plus after 48 hours. A Friedman test was reported as positive.

On the night of April 26, while at home, the patient developed a severe frontal headache associated with blurring of vision and marked vertigo. This was followed by several episodes of vomiting. Shortly thereafter, she developed severe epigastric pain, and the liver was palpable and tender. Blood pressure was 184/118. There was a 2 plus albuminuria. The clinical picture was that of an impending eclampsia, and the patient was given morphine for sedation.

By the following day, she was again symptom-free. No further treatment was given, and the patient had no further such attacks.

On May 29, the Friedman test was repeated and was negative. X-ray of the chest revealed no pleural or pulmonary pathology. The patient had no complaints except for a daily vaginal spotting, varying in color from a pinkish stain to a reddish-brown mucous discharge.

On June 21, pelvic examination revealed the cervix to be formed and closed with no evidence of erosion. The uterus was normal in size, regular in outline, and anterior. No adnexal masses were palpable.

On July 1, another Friedman test was reported as positive. The patient was re-examined ten days later, at which time she stated that the vaginal spotting had become more profuse and was bright red in color. The left ovary now seemed cystic and about twice normal size. The right ovary was slightly enlarged and cystic. Dilution Friedman tests were reported as strongly positive in the concentrated specimen and in the 1:1 dilution. Urine diluted 1:9 was negative in a third Friedman test.

In view of the cystic enlargement of the ovaries and the positive Friedman tests, even on dilution, chorionepithelioma of the uterus was considered; and the patient was again

## HYDATIDIFORM MOLE FOLLOWED BY POSTPARTUM ECLAMPSIA AND CHORIONEPITHELIOMA, WITH RECOVERY

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THE relationship of hydatidiform mole to chorionepithelioma has been the subject of frequent dissertations in medical literature during the past years. However, little mention has been made of the toxemia that is sometimes associated with mole.

In a recent extensive survey of the world literature, Chesley, Cosgrove, and Preece<sup>1</sup> were able to collect only thirty-five cases of probable or alleged eclampsia occurring in association with hydatidiform mole. Only three cases in this series recorded convulsive seizures occurring in the puerperal period.

The authors recently had occasion to treat for hydatidiform mole a patient who developed convulsive seizures on her sixth postpartum day. The convulsions occurred in the presence of an elevated blood pressure, an albuminuria, and edema; and the convulsions were typical of those seen in eclampsia. Recovery was prompt with the usual medical treatment. Four months later the patient developed chorionepithelioma of the uterus, confirmed by surgery. The patient has remained in good health for one year postoperatively, and she shows no evidence of metastases or recurrences.

A complete report of the case is herewith presented:

The patient was a 29-year-old, white, secundigravida whose last normal menstrual period had begun on Nov. 17, 1946. Shortly thereafter, she developed nausea with occasional vomiting, which persisted until the end of February, finally disappearing without treatment.

On Jan. 17, 1947, the patient noted slight, brownish, odorless staining from the vagina, unassociated with backache or cramps. This recurred almost daily, but was never sufficient to necessitate the use of a pad.

Her past history was negative except for a spontaneous complete abortion at two months' gestation, April, 1945.

On March 17, the patient had a profuse vaginal hemorrhage associated with slight cramps and backache. Estimated blood loss was 500 c.c. On March 22, at 5 P.M., the patient had another profuse hemorrhage of approximately 500 c.c., and a similar hemorrhage occurred at 7 P.M. She was admitted to St. John's Hospital shortly thereafter.

On physical examination, the patient appeared extremely pallid. Blood pressure was 180/124, rectal temperature 99.6° F., pulse 108, respirations 20. On abdominal examination, the uterus seemed enlarged to 6 months' gestation, extending two fingerbreadths above the umbilicus. No fetal heart tones could be heard. Palpation of the uterus resulted in further profuse vaginal bleeding. Sterile vaginal examination revealed a well-formed, long cervix which would admit only one finger. The cervix seemed to be pushed anteriorly by a huge, soft, boggy mass filling the entire cul-de-sac. The palpating finger, when inserted into the cervix, encountered a boggy, spongy mass which seemed to cover the entire cervical os. The patient was prepared at once for laparotomy. The pre-operative diagnosis was placenta previa centralis.

Blood loss following admission to the hospital was estimated to be 1,200 c.c. Two pints of whole blood were given to the patient during the operative procedure, having been preceded by three 500 c.c. units of plasma.

well-defined, hyalinized lamina propria. One small cellular aggregation is evident in an immediately adjacent portion of the myometrium. Dilated, thin-walled vascular channels are numerous in and adjacent to the hemorrhagic nodule. There is no additional evidence of further infiltration of the trophoblastic elements beyond the zone noted. The nodule is covered by compact, atrophic endometrium, showing fibrosis of the stroma."



Fig. 2.—Photomicrograph ( $\times 30$ ), showing nodule composed of two hemorrhagic areas, about which are grouped small islands of trophoblastic cells. The nodule is covered by compact, atrophic endometrium showing fibrosis of the stroma.

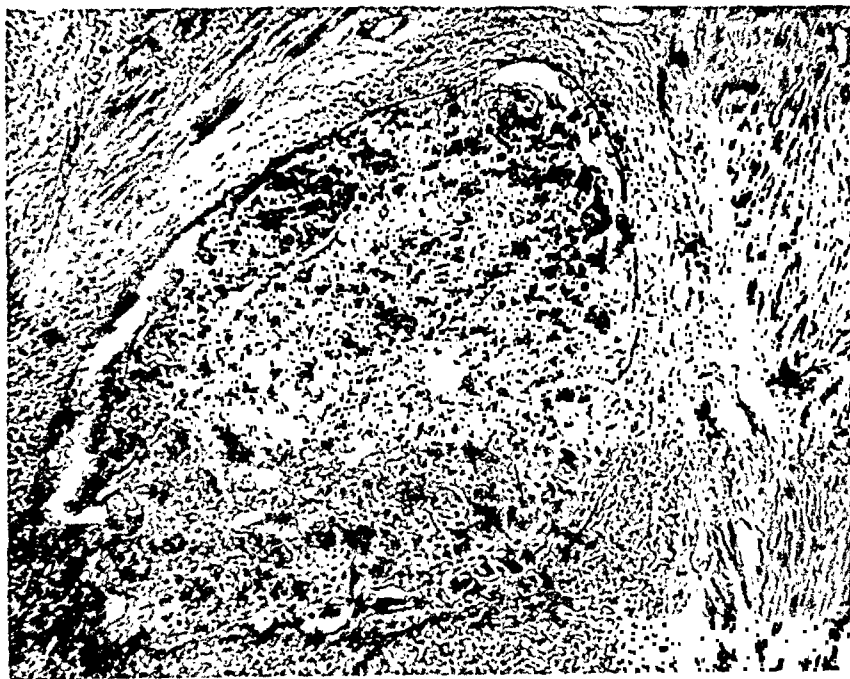


Fig. 3.—Photomicrograph ( $\times 125$ ), showing unit of trophoblastic cells deep in myometrium.

hospitalized. Vaginal smears, taken according to the Papanicolaou technique, were reported by a qualified observer as negative for carcinoma. Pelvic examination was repeated on July 14, and the cystic enlargement of the ovaries seemed to have been progressive.

On July 15, 1947, preceding laparotomy, a dilatation and curettage were done. A minimal amount of normal appearing endometrium was obtained. At laparotomy, the uterus was slightly enlarged, somewhat softer than normal, and of a dark reddish-purple color. The previous hysterotomy was well healed, but a small area of bluish discoloration was noted at the upper angle of the scar. The tubes appeared normal. Both ovaries were the size of lemons, and contained numerous, thin-walled cysts filled with a clear yellow fluid. No enlargement of the pelvic or peri-aortic lymph glands was noted. The liver was palpated and seemed free of metastases. A total hysterectomy and bilateral salpingo-oophorectomy were performed.

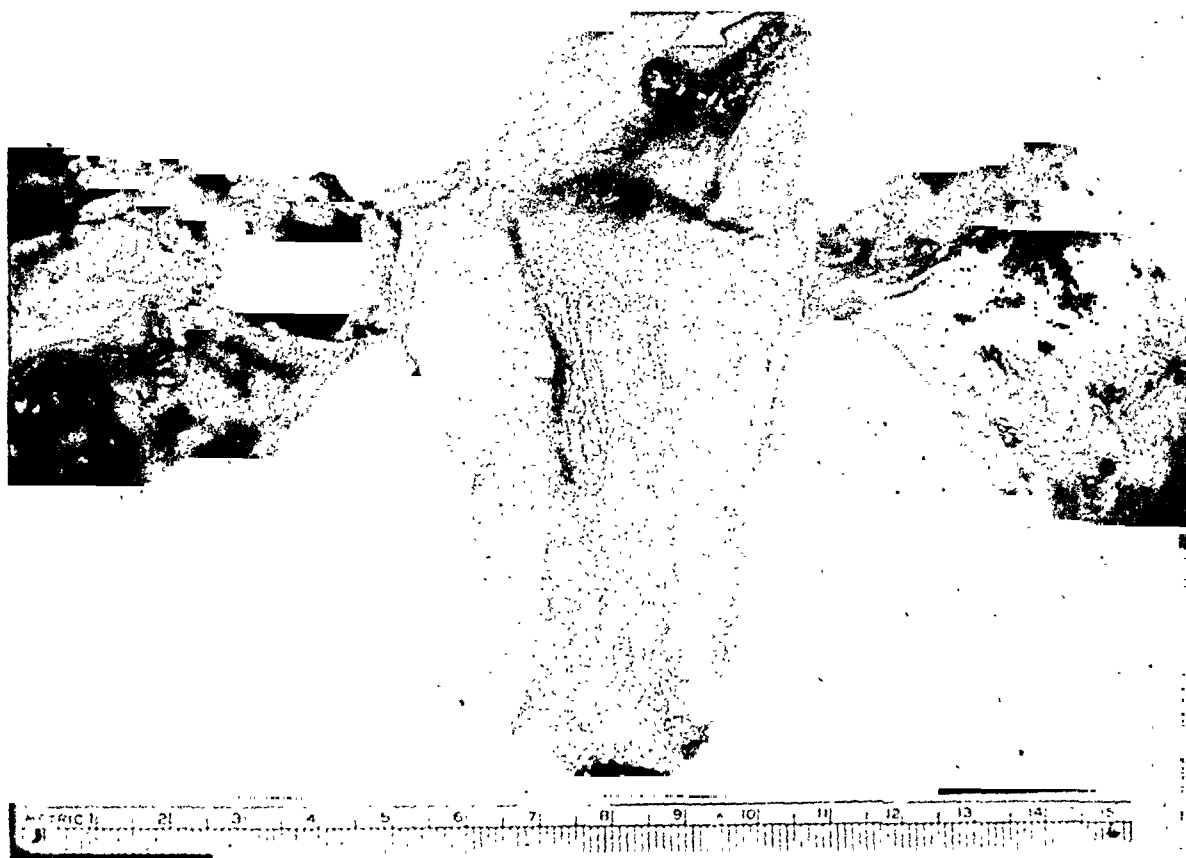


Fig. 1.—Photograph, showing uterus, both Fallopian tubes and ovaries. The uterus has been bisected, and arrow points to hemorrhagic nodule of chorionepithelioma in posterior wall.

On section of the uterus, the endometrial cavity measured 8 cm. in length and varied from 2 to 3.5 cm. in width. The endometrial surface was dark red and granular. The endometrium was less than 1 mm. in thickness. Projecting beneath the endometrium on the posterior wall of the fundus was an ovoid nodule, 0.5 by 0.7 cm., which was dark reddish-purple in color. Microscopic examination through this area was reported as follows:

“The hemorrhagic nodule is composed of groups of trophoblastic epithelial cells surrounding zones of extravasated erythrocytes and poorly defined, necrotic material. The units have a rim of polyhedral and irregular cells with ovoid and lobulated nuclei containing moderately coarse basophilic chromatin granules, and with clear cytoplasm. Granular acidophilic material is evident in some of the peripheral, but more conspicuously in the central portions of the aggregations. Shadows of trophoblastic epithelium can be recognized in some foci. Fibrillar and fibrous tissue surrounds the units, several of which show moderately

tional cases other than the one herewith reported, and H. Acosta-Sison<sup>3</sup> has already called attention to it as a diagnostic aid.

Anterior hysterotomy is recommended as the treatment of choice for hydatidiform mole when the uterus is enlarged beyond a twelve weeks' gestation. As pointed out by Hill,<sup>4</sup> (1) complete removal of the whole mole is possible under direct vision; (2) macroscopic evidence of invasion of the myometrium is available, allowing immediate hysterectomy if indicated; (3) accidental perforation of the uterus is eliminated; and (4) hemorrhage is controllable. Bland,<sup>4</sup> in 1928, reported two deaths from hemorrhage incurred by attempted evacuation of moles through the vaginal route.

The onset of eclamptic convulsions one week after evacuation of the mole was an unusual complication in the case presented. A diagnosis of postpartum eclampsia can only be made by exclusion in the presence of certain signs and symptoms, namely, (1) a history of pre-eclampsia or toxemia during the pregnancy; (2) an elevated blood pressure; (3) albuminuria; (4) edema; and (5) convulsive seizures. In the case reported, all these were present. The patient gave no history of epilepsy, and she has not exhibited any previous or succeeding convulsive attacks. The authors feel that this case represents a true postpartum eclampsia.

The incidence for chorionepithelioma developing subsequent to the treatment for hydatidiform mole is said to be between 2 and 3 per cent, although 50 per cent of patients with chorionepithelioma present a preceding history of hydatidiform mole.

Diagnosis of chorionepithelioma in the case above presented was made early in its onset, and treatment was radical despite minimal signs and symptoms. A reversal of the Friedman reaction after several months of negative results is, of course, highly important. However, a quantitative test positive in 1:1 dilution and negative in 1:9 dilution, suggests a reaction of unusually low titer. Such a rise in titer could be compatible with the development of a new pregnancy. But, and most significantly, a bilateral cystic enlargement of the ovaries was also noted; and observation of these, even over a period of several days, showed a rapid increase in their size.

The patient has continued to remain in good health postoperatively, and will be followed at regular intervals by clinical examination, roentgen studies, and Friedman tests.

The authors feel that the disease has been arrested in the patient by prompt and radical surgical intervention.

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2104 FOSTER AVENUE.

The pathologic diagnosis was chorionepithelioma of the uterus. Histopathologic study of the ovaries revealed numerous lutein and follicular cysts.

Postoperative convalescence was uneventful. Roentgen studies of the skeletal system were made six weeks postoperatively, and they were entirely negative for any metastases. The Friedman reaction was still positive.

On August 23, a pea-sized nodule was palpated for the first time at the site of transfixation of the right round ligament to the vaginal vault. By September 6, this mass seemed almost to have doubled itself in size. Dilution Friedman tests were reported as positive for 1:1 dilution, negative for 1:9 dilution. In view of these, the patient was begun on a course of deep x-ray therapy. Roentgen therapy was completed on October 14, after a total of 2,000 r. to each of four pelvic ports had been given. The Friedman reaction with concentrated urine was negative. By November 13, the pelvic nodule had almost completely disappeared, and pelvic examination was entirely negative.

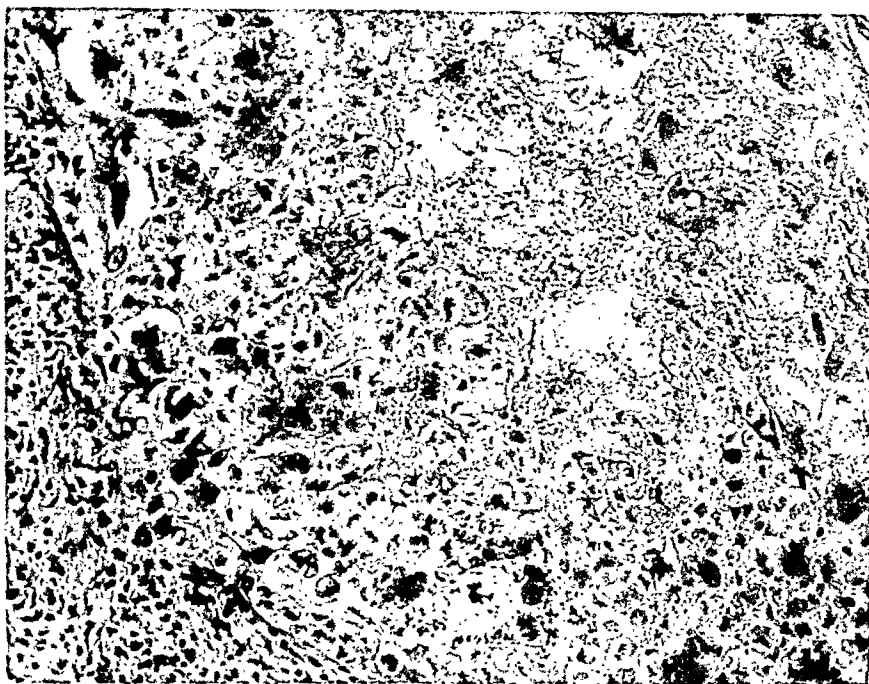


Fig. 4.—Photomicrograph ( $\times 250$ ), showing cytology of trophoblastic island. The center of the aggregation is composed of granular, acidophilic material, among which shadows of trophoblastic epithelium are noted.

The patient has been followed at regular intervals since this time, and she has presented no unusual signs or symptoms. The Friedman tests have remained negative, and general and vaginal examinations have shown no evidence of recurrences or metastases.

### Discussion

Hydatidiform mole occurs once in approximately 1,500 gestations. At Kings County Hospital, Brooklyn, in the ten-year period from 1937 through 1946, the authors found the incidence to be 1 in 1,349 pregnancies. This agrees closely with the incidence of 1 to 1,321 reported by Chesley et al.<sup>1</sup>

Mole is more frequent in multigravidas, and 40 per cent occur in women past the age of 40 years. Essen Moeller<sup>2</sup> states that chorionepithelioma has a greater incidence in this older group, and he recommends that all moles occurring in women past 40, and especially after 45, be treated by hysterectomy.

A fullness of the lower uterine segment with a bulging into the cul-de-sac seems to be an important sign peculiar to hydatidiform mole. This has been noted by us in three addi-

at comparable periods of gestation is consistently lower (Table II). In most of the groups, the infants of a single pregnancy weighed between 500 Gm. and 600 Gm. more than an infant which was one of twins. In the groups at term this difference was 680 Gm.

TABLE I. DIFFERENCE IN WEIGHT IN THE TWO TWINS IN RELATION TO LENGTH OF GESTATION

LENGTH OF GESTATION FROM FIRST DAY OF LAST MENSTRUAL PERIOD	NUMBER OF CASES	PER-CENTAGE OF CASES	MEAN WEIGHT	STANDARD OF DEVIATION	AVERAGE DIFFERENCE IN WEIGHT OF FIRST AND SECOND TWIN	STANDARD OF DEVIATION
Total pregnancies	249	100.	2,354.1	703.9		
Term (265-295 days)	109	43.8	2,737.7	479.6		
160-169	2	0.8	583.8	157.0	76.5	38.5
170-179	3	1.2	749.2	98.3	95.0	37.7
180-189	3	1.2	790.0	74.9	130.0	112.8
190-199	3	1.2	927.5	334.1	161.7	98.0
200-209	6	2.4	951.3	291.03	219.3	321.8
210-219	9	3.6	1,372.6	472.44	337.0	220.6
220-229	5	2.0	1,685.5	567.4	177.0	59.3
230-239	14	5.6	1,989.3	534.0	397.9	622.1
240-249	32	12.8	2,270.6	477.5	300.8	311.3
250-259	39	15.7	2,371.2	457.38	308.4	440.1
260-269	43	17.3	2,525.2	447.2	375.8	336.0
270-279	44	17.7	2,753.6	530.66	521.6	494.8
280-289	35	14.1	2,877.6	406.94	385.1	297.5
290-299	10	4.0	2,588.0	448.55	451.0	230.2
300-310	1	0.4	2,220.0	65.0	130.0	0

TABLE II. WEIGHT IN RELATION TO LENGTH OF GESTATION IN COMPARISON TO WEIGHT OF SINGLE INFANTS

LENGTH OF GESTATION FROM FIRST DAY OF LAST MENSTRUAL PERIOD	SINGLE PREGNANCIES 1,000 CASES		TWIN PREGNANCIES 249 CASES	
	PREGNANCY PER CENT	MEAN WEIGHT (GM.)	PREGNANCY PER CENT	MEAN WEIGHT (GM.)
Total pregnancies	100.	3,405.8	100.	2,354.1
Term (265-295 days)	77.55	3,418.3	43.8	2,737.7
160-169			0.8	583.8
170-179			1.2	749.2
180-189			1.2	790.0
190-199			1.2	927.5
200-209			2.4	951.3
210-219			3.6	1,372.6
220-229	0.7	2,716.6	2.0	1,685.5
230-239	0.6	2,050.0	5.6	1,989.3
240-249	1.92	2,923.6	12.8	2,270.6
250-259	2.43	3,133.3	15.7	2,371.2
260-269	9.5	3,098.9	17.3	2,525.2
270-279	27.4	3,325.0	17.7	2,753.6
280-289	31.85	3,591.0	14.1	2,877.6
290-299	19.21	3,618.6	4.0	2,588.0
300-309	4.15	3,650.0	.4	2,220.0
310-319	1.84	3,556.0		
320 plus	.40	3,777.0		

*Length of Gestation.*—The average length of gestation in 1,000 unselected single pregnancies reported by Potter and Crunden<sup>1</sup> was 281 days. In this series the mean length of gestation for 249 twin pregnancies was 256.7 days. In 63.5 per cent (158) of the cases, one or both infants weighed more than 2,500

## MULTIPLE PREGNANCIES AT THE CHICAGO LYING-IN HOSPITAL, 1941 TO 1947

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IN NOVEMBER, 1941, Potter and Crunden<sup>1</sup> reported on 283 multiple pregnancies observed at the Chicago Lying-in Hospital between May 25, 1931, and Jan. 1, 1941. There were 281 sets of twins and 2 sets of triplets in this group. The present study covers an interval of six and one-half years, extending from Jan. 1, 1941, to July 1, 1947. During this period 22,943 women were delivered in this hospital. The deliveries included 257 multiple pregnancies, of which there were 252 sets of twins and five sets of triplets. This makes an incidence of 1:88.8 for multiple pregnancy, 1:91.0 for twins, and 1:4,588 for triplets. The incidence for twins born in the hospital in the previous series was also 1:91. The incidence of twins in both series is slightly lower than that of 1:87 which is given for the United States as a whole.

**Parity.**—In this series, 35.0 per cent (91) of the women with multiple pregnancies were primigravidas, 33.9 per cent (87) were in their second pregnancy, 14.5 per cent (37) in their third, 7.9 per cent (20) in their fourth, 2.0 per cent (5) in their fifth, 2.3 per cent (6) in their sixth and 2.8 per cent (7) in their seventh pregnancy. The remaining four women (1.6 per cent) had twins in their eighth, ninth, tenth, and eleventh pregnancies, respectively. In the entire group there were three women who had had previous sets of twins. Two of these had twins in their third and fourth pregnancies and the other produced twins in her seventh and ninth pregnancies. Forty-three per cent (9,924) of all the women delivered during this interval were primigravidas. The incidence of multiple births is only 1:109 in first pregnancies in comparison to 1:78 in subsequent pregnancies.

**Birth Weight in Relation to Length of Gestation.**—The data on gestational age and birth weight are based on 249 sets of twins, inasmuch as the menstrual age was not obtainable in three of the twin pregnancies. Seventy-seven and six-tenths per cent (193) of the women in this series delivered between the 240th and the 289th day, 4.4 per cent (11 cases) went past the 289th days and 18 per cent (45 cases) delivered before the 240th day, as calculated from the first day of the last menstrual period. Forty-three and eight-tenths per cent (109) of these mothers had their babies between the 265th and 295th day, within the period usually considered at term. The mean weight of infants born during this period was 2,737.7 Gm. The average difference in weight between the first and second twin was roughly 400 to 500 Gm. in the twins born between the 260th and 290th day. This difference was smaller in the groups of younger gestational age. The mean weights and average differences in weight between the twins for the various age groups are shown in Table I. As would be expected when compared with a group of 1,000 single pregnancies, the mean weights of twins born



raceous twin, was undetermined. Fused monochorionic twin placentas are ordinarily thought to indicate that the twins arose from a single ovum but in this series there were two sets of twins of different sexes in the group of 48 fused monochorionic placentas. There were no monoamniotic twin placentas, except for the twin papyraceous fetuses in the triplet pregnancy. The cords in this instance were extremely tangled and this was presumably responsible for fetal death.

Based on the 149 twin placentas for which complete information including weight is available, the average ratio between the weight of the placenta (without cord and membranes) and the combined birth weight of the twins was 1:6.7. This ratio is almost the same in the separate as in the fused placentas. In cases where the placentas were separate, the average ratio was 1:6.66 and in the fused group it was 1:6.72. This ratio, as in the first series of twins reported from this institution is slightly lower than the average for single pregnancies of 1:7.1 reported by Adair and Thelander.<sup>2</sup> In this series the ratios varied from 1:2.3 to 1:13.1. In general, the smaller babies were associated with proportionately larger placentas and vice versa. The largest set of twins in this series had a combined weight of 7,440 Gm. the placenta weighed 1,183 Gm. and the ratio was 1:6.3. It is obvious that there is a wide margin of safety in the amount of placental tissue necessary to provide adequate circulation for the infants.

The triplet placentas included one which was completely fused and four which consisted of two fused plus a single placenta. The (1) completely fused placenta was monochorionic and triamniotic; the fused placentas associated with the single placentas were (2) monochorionic and monoamniotic, (3) monochorionic and diamniotic, (4) dichorionic and diamniotic and (5) unrecorded. The infants in the five cases were (1) all female, (2) one female and two unknown, (3) and (4) one female and two males, and (5) all female. The average ratio of the weight of the placenta to the combined weight of the infants was 1:4.4.

*Position.*—In 44 per cent (111) of all cases, both babies were in a cephalic presentation. In 7.9 per cent (20), they were both breech. In 26.2 per cent (64), the first baby was cephalic and the second breech, while the reverse condition occurred in 13.19 per cent (33) of the cases. In 6.7 per cent (7) the second baby was in a transverse position and presented by the scapula or arm; 67.2 per cent (339) of the total of 504 babies were cephalic presentations and 28.3 per cent (143) were breech. Eighty-six second twins presented by the breech, in contrast to 57 first twins with a similar presentation. More first twins (194) had cephalic presentations than second twins (145). The frequency of the various presentations are shown in Table IV.

TABLE IV. POSITION OF TWINS AT DELIVERY

FIRST TWIN	SECOND TWIN	NUMBER OF CASES	PER CENT
Cephalic	Cephalic	111	44.1
Cephalic	Breech	66	26.2
Cephalic	Compound	13	5.1
Cephalic	Unrecorded	4	1.6
Breech	Breech	20	7.9
Breech	Cephalic	33	13.1
Breech	Compound	4	1.6
Compound	Cephalic	1	.4
Total		252	100.
Total infants with cephalic presentation		339	67.2
Total infants with breech presentation		143	28.3
Total infants with compound presentation		18	3.5
Total infants with no record		4	1.0
Total infants		504	100.

Gm. and in this group the mean length of gestation was 269.4 days. The length of gestation is correlated with the combined weights of the babies in Table III. The correlation with weight groups is better when this method is used than when the larger infant determines the grouping. The mean gestational age for the 47.7 per cent of cases in which the infants had a combined weight over 5,000 Gm. was 271.2 days. The average gestational age for single infants weighing approximately 2,500 Gm. is about 267 days.

TABLE III. LENGTH OF GESTATION IN RELATION TO COMBINED WEIGHT OF TWINS\*

COMBINED WEIGHTS OF INFANTS IN GM.	NO. OF CASES	PER CENT OF CASES	MEAN LENGTH OF GESTATION	STANDARD OF DEVIATION
Total pregnancies	254	100.0	256.2	27.32
Term (those with total weight over 5,000 Gm.)	121	47.7	271.2	13.80
500-999	2	.79	227.5	15.50
1,000-1,499	9	3.55	183.4	19.67
1,500-1,999	6	2.36	192.7	11.36
2,000-2,499	4	1.57	226.8	20.86
2,500-2,999	11	4.34	221.9	22.08
3,000-3,499	11	4.34	237.3	23.95
3,500-3,999	17	6.70	249.4	21.80
4,000-4,499	34	13.39	253.2	17.23
4,500-4,999	39	15.34	261.8	14.81
5,000-5,499	44	17.31	268.0	14.45
5,500-5,999	46	18.10	272.1	12.83
6,000-6,499	19	7.48	276.2	11.45
6,500-6,999	10	3.94	271.2	13.19
7,000-7,499	2	.79	275.0	4.00

\*Table is based on 249 twin pregnancies and 5 triplet pregnancies.

*Sex Ratio.*—Two of the 252 sets of twins consisted of a full-term male infant plus a papyraceous twin whose sex was not determined. In the remaining 250 sets, the infants were of the same sex in 170 pairs and of the opposite sex in 80 pairs (female born first in 44, male born first in 36). Of the 170 pairs in which both infants were of the same sex, 85 pairs were boys and 85 pairs were girls. Thus, in 250 pairs of twins there were 250 boys and 250 girls. Most of these twins were born during the war years when popular legend tells us that more than the usual number of boys are born. In this series the ratio of females to males is higher than that of 100:105 given by the United States Bureau of Vital Statistics for total births in the United States. It is also considerably higher than the ratio of 100:117 for the earlier series of twins reported from the Chicago Lying-in Hospital.<sup>1</sup>

One of the five sets of triplets consisted of a full-term female infant plus papyraceous twins whose sex was not determined. There were two sets in which all the babies were females while the remaining two sets each consisted of two boys and a girl.

*Placenta.*—Of the 252 twin placentas, complete descriptions including the type of membranes and weight were available in 149. In 62 cases, a record of the type of placenta and membranes was present but the placenta was not weighed while in the remaining 41 cases no record of the placenta is available. The placenta was recorded as being double in 90 cases, single or fused in 121 cases, with no record in 41 cases. Of the 121 fused placentas, 73 were dichorionic and 48 were monochorionic. In the series of 90 double placentas, there were 52 sets of twins of the same sex and 38 sets in which the babies were of the opposite sex. The 73 fused dichorionic placentas were associated with 40 sets of twins in which the infants were of the same sex and 32 sets of twins of opposite sex. In this group there was one set in which the sex of one fetus, a papy-

highest mortality (23.07 per cent) occurred in the spontaneous breech deliveries, while the next highest mortality (10.63 per cent) was in the group of breech extractions. It is interesting to note that the mortality in the group of spontaneous cephalic deliveries is 10.53 per cent and in a group almost as large delivered by low or outlet forceps the mortality was 4.2 per cent. This is due largely to the fact that forceps were rarely applied to the heads of the very small infants. Fortunately, there were no deaths in the twelve infants delivered by mid and high forceps. The infants delivered by version and extraction, all but one of whom were second twins, showed a mortality of 5.94 per cent for the group. The infant mortality for the cesarean section group (15 sections) was 3.57 per cent.

It has been suggested at times that the second twin is subjected to less hazard than the first because it passes through an already dilated birth canal; it has been thought by others to have a poorer chance of survival because of the possibility of placental detachment following the birth of the first twin. Among the 28 nonmalformed, nonmacerated fetuses and infants weighing over 1,000 Gm. who died or were stillborn, 15 were first born, 13 were second born. The difference is not significant.

TABLE VI. MORTALITY IN RELATION TO METHOD OF DELIVERY

METHOD OF DELIVERY	NUMBER OF BIRTHS		STILLBIRTHS AND NEONATAL DEATHS		
	FIRST TWIN	SECOND TWIN	WEIGHT UNDER 1,000 GM.	WEIGHT OVER 1,000 GM.	PER CENT MORTALITY OVER 1,000 GM.
<i>Cephalic.</i> —					
Spontaneous	89 (2) *	42 (2)	17 (1)	12	10.5
Low and outlet forceps	95	24	0	5	4.2
Mid forceps and high forceps	2	10	0	0	0
Version and extraction	1	84 (1)	1	5 (1)	5.9
<i>Breech.</i> —					
Spontaneous	24 (1)	10	8	6 (1)	23.1
Breech extraction	31 (2)	73 (5)	10 (3)	10 (1)	10.6
<i>Cesarean section</i>	15	15	2	1	3.6
<i>No record</i>	0	4 (2)	4 (2)	0	0
Total	257 (5)	262 (10)	42 (6)	39 (3)	8.1

\*Triplets in parentheses.

*Mortality in Relation to Cause of Death.*—Table VII. All of the infants who failed to survive were subjected to postmortem examination except one in whom a clinical diagnosis of pneumonia was made. More than half of the infants (46) showed no abnormalities other than those associated with inadequate pulmonary function. Seven babies showed evidence of anoxia in the form of petechial hemorrhages of the lungs, heart, and thymus. Congenital anomalies were present in six. Three of these had multiple anomalies, one had a congenital muscular defect in the stomach which was responsible for rupture, one a spina bifida, and one a tracheo-esophageal fistula. In none of the cases did both twins exhibit anomalies. One of the infants with multiple anomalies was a triplet. Pulmonary hemorrhage was found in six instances, pneumonia in four. Five babies of three twin pregnancies died of erythroblastosis. Both died after birth in one pregnancy, one died and one was stillborn in the second, and one died and one survived in the third. Another set of twins weighing less than 1,000 Gm. exhibited mild general edema but a diagnosis of erythroblastosis could not be made. Intracranial hemorrhage was demonstrated in only two instances.

### Fetal and Infant Mortality

Eighty-one of the 519 fetuses and infants resulting from 257 multiple pregnancies were stillborn or failed to survive the neonatal period (Table V). The eighty-one deaths include five abortions (under 400 Gm.), 29 stillbirths and 47 neonatal deaths. There were two sets of twins in which one fetus was listed as an abortion (under 400 Gm.), one set of triplets in which two were abortions (papyraceous twins), and one set of triplets in which one fetus was under 400 Gm.

TABLE V. MORTALITY IN RELATION TO WEIGHT

WEIGHT IN GM.	TOTAL BIRTHS	NEONATAL DEATHS	STILLBIRTHS	TOTAL NUMBER	MORTALITY PER CENT
2,500 and over	245 (1)*	2	2	4	1.6
2,000-2,499	146 (2)	5	5	10	6.8
1,500-1,999	51 (1)	3	3	6	11.8
1,000-1,499	34 (4)	16 (3)	3	19 (3)	55.9
400-999	38 (4)	21 (3)	16	37 (3)	97.4
Under 400	5 (3)		5 (3)	5 (3)	100.00
Total	519 (15)	47 (6)	34 (3)	81 (9)	15.6

\*Triplets in parentheses.

The total uncorrected mortality for this series is 15.6 per cent. If the abortions and fetuses weighing less than 1,000 Gm. are excluded, the mortality is 8.2 per cent, and if those under 1,500 Gm. are excluded, it falls to 4.4 per cent. This latter figure is twice the total hospital mortality of 2.0 per cent which existed during the same period for infants and fetuses weighing over 1,500 Gm. Among those who weighed over 2,500 Gm., only 2 deaths and 2 stillbirths occurred. This is a rate of 1.6 per cent which is identical with that for single infants born during the same period. It is a common belief that a twin infant weighing under 2,500 Gm. is smaller than a single infant of equivalent gestational age and consequently is proportionately less premature and less handicapped than a single infant of equal size. These data seem to disprove that supposition, for twin infants weighing from 1,500 to 2,500 Gm. show over twice the mortality of single infants in the same weight groups; those weighing over 2,500 Gm. do not appear to be handicapped by the fact of being a twin.

*Mortality in Triplets.*—In only one set of triplets did all of the infants survive the neonatal period. These babies were all girls and weighed 2,360 Gm., 2,350 Gm., and 1,755 Gm. at birth. One set consisted of a full-term female infant weighing 3,190 Gm. and papyraceous twins which weighed 61 Gm. and 68 Gm., respectively. Another set, in which the weights were 470 Gm., 420 Gm., and 390 Gm., all died. None of the infants survived in an older set with weights of 1,160 Gm., 1,120 Gm., and 1,040 Gm. In the fifth set, the weights were 1,019 Gm., 885 Gm., and 920 Gm. The third baby in this group died during the neonatal period. The second one lived four months and the one weighing the most died at the age of five and one-half months. Of the fifteen babies included in five triplet pregnancies only six survived the neonatal period, and only four were alive at six months.

*Mortality in Relation to Mode of Delivery.*—(Table VI.) Of the infants in a cephalic presentation, 131 were delivered spontaneously, 119 by low or outlet forceps, 10 by midforceps, and two by high forceps. Of those with a breech presentation, 34 were delivered spontaneously, and 104 by extraction. Eighty-five infants were delivered by version and extraction (68 cephalic and 17 transverse) and 30 were delivered by the abdominal route. Considering only the stillbirths and neonatal deaths among infants weighing over 1,000 Gm., the

tension or pre-eclampsia. Eclampsia did not occur in any of the cases. There was one maternal death in the series resulting from bacterial endocarditis with mitral stenosis and insufficiency, a maternal mortality of 0.39 per cent.

Cesarean sections were performed in fifteen cases. The maternal indications were as follows: previous section in six cases, pre-eclampsia two, placenta previa two, elderly primigravida with fibroids one (cesarean hysterectomy), elderly primigravida with hypertensive toxemia one, hypertensive toxemia with chronic renal disease one, essential hypertension one, and one case was sectioned after a twenty-two hour labor without progress.

### Summary

In the six and one-half year period prior to July 1, 1947, there were 22,943 deliveries at the Chicago Lying-in Hospital. Among these there were 257 multiple pregnancies, an incidence of 1:91 for twins and 1:4,580 for triplets.

The mean birth weight in this series was 2,354 Gm.

The mean length of gestation for twin pregnancies was 256.7 days and for multiple pregnancies (including triplets) in which the combined weight of the babies was over 5,000 Gm. is 271.2 days.

The mortality for all infants and fetuses weighing more than 1,000 Gm. was 8.2 per cent and for those over 2,500 Gm. was 1.6 per cent. The mortality for single infants born in this hospital during the same period was 2.5 per cent over 1,000 Gm. and 1.6 per cent over 2,500 Gm.

The mean ratio between the weight of the placenta and the combined birth weight of the twins was 1:6.7, a ratio only slightly different from that of 1:7 found for single infants.

The twins associated with 48 monochorionic placentas were of the same sex in 46; of different sexes in 2. Those associated with dichorionic placentas were of the same sex in 92, of different sexes in 70.

The incidence of pre-eclamptic and hypertensive toxemia in this series was 21 per cent, in comparison to approximately 8 per cent for all deliveries. Post-partum hemorrhage and polyhydramnios also occurred more frequently than in single pregnancies.

Prematurity was the most important cause of death in this series of twin infants. Polyhydramnios, placenta previa, and abruptio placentae were the maternal complications most commonly associated with fetal mortality.

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Resorption atelectasis, with the formation of a hyaline membrane, was found twice. In two cases, perirenal hemorrhage was present; in one instance, it was associated with a hematoma of the liver.

TABLE VII. CAUSE OF DEATH IN RELATION TO WEIGHT

	STILLBIRTHS		DEATHS		TOTAL
	1ST TWIN	2ND TWIN	1ST TWIN	2ND TWIN	
Over 2,500 Gm.—					
Anoxia	1			1	2
Erythroblastosis	1			1	2
1,000 to 2,500 Gm.—					4
No abnormalities	1	6	2 (1)*	4 (2)	13
Anoxia	2	1	1	1	5
Pulmonary hemorrhage			3	1	4
Intracranial hemorrhage			1	1	2
Erythroblastosis		1	2		3
Pneumonia			2	2	4
Malformations			3	1	4
Under 1,000 Gm.—					35
No abnormalities	8	11 (3)	7	10	36
Anoxia		1	1 (1)		2
Pulmonary hemorrhage				1	1
Hepatic hemorrhage				1 (1)	1
Malformations		1		1 (1)	2
Total	13	21 (3)	22 (2)	25 (4)	81

\*Triplets in parentheses.

*Maternal Complications.*—The belief that maternal complications are of increased frequency in multiple pregnancy is well borne out in this series. One hundred ten of the two hundred fifty-seven mothers had one or more complications during their pregnancies. Pre-eclampsia, the most common complication, was present in 39 cases, an incidence of 15.17 per cent, and an additional 5.84 per cent (15 cases) exhibited hypertensive toxemia in which an existing hypertension was aggravated by the pregnancy. Each of three women with pre-eclampsia and 1 with hypertension lost one infant; an additional mother with hypertension lost both infants. Four had one infant survive. This is a mortality rate of only 4.5 per cent for the 108 infants delivered by these women with pre-eclamptic or hypertension toxemia.

Anemia with a hemoglobin below 10 Gm. and contracted pelvis were each present in 13 cases. None of these mothers lost an infant.

Polyhydramnios occurred in 11 pregnancies and of all the maternal complications it seems to be the only one, other than placenta previa and abruptio placentae, that is associated with a significant increase in fetal mortality. Twelve fetal and neonatal deaths were associated with the eleven pregnancies which exhibited an abnormal increase in amniotic fluid. The high infant mortality associated with polyhydramnios is due mainly to prematurity. Nine of these fetuses and infants weighed less than 1,000 Gm., one weighed 1,300 Gm., one weighed 2,015 Gm. and had a spina bifida, and one weighed 2,375 Gm. and was badly macerated.

Premature detachment of the placenta occurred in four cases, placenta previa in three. Four fetal deaths were associated with premature placental detachment and two with placenta previa. Postpartum hemorrhage was found 26 times, an incidence of 10 per cent. The frequency is thought to be a result of poor contraction resulting from hyperdistention of the uterus.

Thirty of the 110 mothers had more than one complication, the most frequent combination being postpartum hemorrhage associated with either hyper-

were taken in each instance for an average period of 10 days (240 hours). Approximately 900 vaginal smears have been studied. Details related to the technique of taking the smears, the staining method and the daily tabulation of observations have been described previously.<sup>1</sup>

## Results

Eight women received injections of estradiol dipropionate in sesame oil, four of estradiol benzoate in peanut oil and three of estradiol benzoate in propylene glycol. Estradiol in aqueous suspension was administered to sixteen subjects, estradiol in sesame oil to three, and estradiol in propylene glycol to two. Estrone in aqueous suspension was employed in 20 instances (Tables I and II).

Thirty-two of the 57 injections of estrogen were followed by a follicular response in the vaginal epithelium which was undoubtedly due to the hormone administered. In addition, seven tests, in four women, produced questionable results. These included Cases 3A and 18A, women exhibiting cyclic ovarian activity prior to the study; Case 1A, in whom one test dose of hormone produced cytological alterations in the vaginal epithelium not sufficiently definitive for classification; and Case 14A, in whom previous therapy had apparently resulted in "priming" of the vaginal mucosa. These four cases have been previously reported and will be given no further consideration here.<sup>2</sup> In eighteen instances, the vaginal smears were not altered by the injection of the estrogen. Among these were five patients who had received estradiol dipropionate in sesame oil; two, estradiol benzoate in propylene glycol; one, estradiol in sesame oil; three, estradiol in aqueous suspension; and seven, estrone in aqueous suspension.

1. *Lag-Time*.—The lag-time varied from 48 to 168 hours (Table II). Had we accepted the earliest evidence of a change in the vaginal smear as indicative of estrogenic activity, this period might have been somewhat shortened. However, some false positive reactions would also have been reported. It seemed best to adhere strictly to the grading of the degree of response from 1 plus to 4 plus according to the criteria noted in the footnote to Table I. In the average patient, four to five days were usually required to elicit such a quantitative reaction. This lag-period was not dependent on the type of estrogen administered. Of the five subjects tested with an estrogen in propylene glycol, three showed a response in the vaginal smear with an average lag-time that was slightly longer than that noted following the use of an estrogen in oil or water. Similar results have been obtained in connection with a larger series of patients in whom greater amounts of estrogen were administered in the corresponding media,<sup>1</sup>

2. *Duration of Estrogenic Effect*.—The over-all variation in the duration of the estrogenic response ranged from 24 to 192 hours (Tables I and II). It

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\*Status: PM — Postmenopausal

M — Menses have ceased within a three-year period

SC — Surgical Castrate

SO — Single oophorectomy and hysterectomy

Me — Menstruating

Numbers in parentheses denote number of years since cessation of menses.

Rx:

A — 1 mg. estradiol dipropionate in sesame oil

B — 1 mg. estradiol benzoate in peanut oil

C — 1 mg. estradiol benzoate in propylene glycol

D — 1 mg. estradiol in sesame oil

E — 1 mg. estradiol in propylene glycol

F — 1 mg. estrone in aqueous suspension

G — 1 mg. estradiol in aqueous suspension

Degree: CCT = change in cell type

+ = 10 — 25% cornification

++ = 25 — 50% cornification

+++ = 50 — 75% cornification

++++ = 75% and over of cornified cells present

# THE EFFECTS OF VARIOUS ESTROGENIC PREPARATIONS

## III. The Influence of Equivalent Amounts of Several Estrogens on the Vaginal Mucosa of Nonmenstruating Women

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IT IS the purpose of the present investigation to observe the effects of a *single* injection of a variety of estrogenic preparations, and to compare them with each other. Emphasis has been placed upon three features which can be measured objectively by a study of the vaginal smear: (1) the "lagtime," i.e., the number of hours between injection of the hormone and the appearance of changes in the vaginal secretion indicative of an estrogenic response; (2) the degree of stimulation; and (3) its duration. Concomitantly, attention has been given to changes in subjective symptomatology in all patients except those who were postmenopausal women entirely free of climacteric symptoms.

### Methods and Procedure

Forty-one women, ranging from 24 to 78 years of age, were subjects of the study. Of these, fourteen were postmenopausal, sixteen, surgical castrates, and nine, menopausal. Of the two remaining subjects, one had had a unilateral oophorectomy and hysterectomy, and the other, at 46 years of age was menstruating regularly but had complaints characteristic of the menopausal syndrome. The group classified as "menopausal" included those women whose menses had ceased within the preceding 3 years and whose symptomatology was distinctly climacteric.

Several of the subjects received injections of two preparations so that a total of 57 studies was made. In all instances in which patients received more than one preparation, an interval of not less than three weeks was allowed to elapse between administration of the two doses. In this way, any "priming" effect of the first injection upon the vaginal mucous membrane was minimized.

The estrogenic preparations\* included estradiol as a solution in sesame oil and propylene glycol and as a suspension in water; estradiol dipropionate in sesame oil; estradiol benzoate in peanut oil and in propylene glycol; and estrone in aqueous suspension. Estradiol, in free and esterified form, was administered in 1 mg. doses and estrone in 4 mg. doses, as previous studies had indicated a weight-for-weight activity ratio of that degree.<sup>1, 2</sup>

In each case, vaginal smears were taken daily for an average of one week prior to the administration of estrogen. From a study of these each patient was classified as to smear type according to the criteria of Papanicolaou and Schorr,<sup>3</sup> when these applied. Changes subsequent to therapy were evaluated in the light of these initial observations. Following injection of the hormone, daily smears

\*All estrogenic preparations used in these studies were furnished by Dr. Edward L. Henderson of the Schering Corporation, whose courtesy is herewith gratefully acknowledged.



TABLE II. CHARACTERISTICS OF THE VAGINAL RESPONSE OF NONMENSTRUATING WOMEN TO SINGLE DOSES OF ESTROGENIC PREPARATIONS\*

TO-TAL	RE-ACT-ING	DRUG	MENSTRUUM	DOSE (MG.)	LAG-TIME (HOURS)		DURATION (HOURS)	
					RANGE	AVERAGE	RANGE	AVERAGE
8	3	Estradiol	Sesame oil	1	60-102	88	30-159	100
		dipropionate						
4	4	Estradiol	Peanut oil	1	102-108	90	30-138	82
		benzoate						
3	1	Estradiol	Propylene glycol	1	120		24	
		benzoate						
3	2	Estradiol	Sesame oil	1	96-120	108	24-48	36
2	2	Estradiol	Propylene glycol	1	108-120	114	108-132	120
21	10	Estrone	Aqueous suspension	4	48-168	100	72-192	110
16	10	Estradiol	Aqueous suspension	1	48-120	90	48-168	109

\*Questionable responses are not included in this table.

was longest on the average in the case of free estradiol administered in a menstruum of propylene glycol (120 hours). With this exception, all preparations in watery suspension produced a more prolonged effect than the solutions in oil or propylene glycol. This may be attributed to the fact that the hormone in situ is not in a soluble state. However, the individual variations were considerable and do not warrant any far-reaching conclusion. The condition of the subject at the time of injection undoubtedly played no little role in the pattern of the response elicited.

3. *The Degree of Vaginal Response.*—Inspection of the individual case records (Table I) shows that, in almost every instance, the degree of the follicular reaction attained can be directly correlated with its duration. Neither duration nor degree of stimulation can be closely related to the type of estrogen administered in the *individual case*.

4. *A Comparison of the Effects of Estrone and Estradiol in Aqueous Suspension.*—To each of fifteen subjects, either estrone or estradiol was administered in aqueous suspension. Not less than three weeks later, after the vaginal smear showed a reversal to the pretreatment status, the second estrogen was given and vaginal changes again observed.

As previously mentioned (Table I), the changes in the vaginal mucosa were of such a nature that their relationship to the administration of the estrogen could be questioned in Cases 3a, 14a, and 18a (Table III).

In some instances, one estrogen was employed first, in others, the second. The order of their usage appeared to make little difference in the results obtained. For instance, four women, who first received estrone, failed to react objectively, whereas the subsequent injection of estradiol was followed by a follicular response in the vaginal smears. This might suggest that the primary injection of hormone had a "priming" effect, not necessarily apparent in the vaginal epithelium, and that the second injection produced noticeable changes because it acted upon an already partially receptive membrane. However, in one case, No. 19A, estrone, the first injection, caused a follicular reaction while, following subsequent treatment with estradiol, the smears showed no alterations in cytological features. Similarly, in Case 1A, estrone produced transient changes in the vaginal epithelium and a later injection of estradiol brought about no response. One cannot, therefore, attach too much significance in this series of experiments to the order in which the preparations were employed.

TABLE I. DATA FROM 41 NONMENSTRUATING WOMEN RECEIVING A SINGLE INJECTION  
OF AN ESTROGEN

RESPONSE								
NO.	AGE	STATUS*	SMEAR TYPE	R *	LAGTIME (HOURS)	DURA- TION (HOURS)	DEGREE*	OBSER- VATION PERIOD (HOURS)
1	52	PM (6)	Pseudoleucopenic	A	-	-	-	132
2	55	PM (7)	Intermediate	A	-	-	-	132
3	70	PM (30)	Atrophic	A	-	-	-	132
4	78	PM (29)	Atrophic	A	-	-	-	132
11	43	SC (9)	Atrophic	A	-	-	-	168
53	49	SC (3)	Intermediate	A	102	30	+	144
54	49	M	Mucous	A	102	111	++	219
55	46	M	Premenstrual	A	60	159	++++	219
19	68	PM	Pseudoleucopenic	B	48	?	+++	60
47	62	PM	Pseudoleucopenic	B	102	138	+	264
48	66	PM	Pseudoleucopenic	B	102	78	++	264
49	60	PM	Atrophic	B	108	30	+	264
57	52	PM (5)	Mucous	C	120	24	+	264
60	54	PM (6)	Pseudoleucopenic	C	-	-	-	264
63	61	PM (9)	Mucous	C	-	-	-	264
50	49	SC (11)	Pseudoleucopenic	D	120	24	+	219
51	53	M	Premenstrual	D	-	-	-	144
52	47	M	Premenstrual	D	96	48	++	144
59	54	PM (6)	Pseudoleucopenic	E	108	132	+	264
65	58	PM (12)	Premenstrual	E	120	108	+	264
1a	54	M	Intermediate	F	-	-	CCT	188
2a	41	SC (2)	Mucous	F	-	-	-	292
3a	46	Me	Cyclic	F	?	?	?	264
4a	61	PM (28)	Premenstrual	F	96	72	+	264
5a	24	SC (2)	Premenstrual	F	48	192	+++	264
6a	48	M	Pseudoleucopenic	F	-	-	-	264
8a	41	SC (2)	Premenstrual	F	96	96	++	264
10a	42	SC (6)	Premenstrual	F	-	-	-	144
11a	52	SC (22)	Premenstrual	F	120	148	+++	264
12a	52	M	Premenstrual	F	168	84	++	264
				F	96	120	+	240
13a	48	M	Premenstrual	F	-	-	-	264
14a	52	M	Intermediate	F	?	?	+++	216
15a	28	SC (1)	Premenstrual	F	-	-	-	264
16a	33	SC (6)	Intermediate	F	96	152	+++	336
18a	37	SC	Cyclic	F	?	?	?	264
19a	28	SC (4)	Premenstrual	F	120	72	+	336
20a	53	SC (7)	Pseudoleucopenic	F	72	96	++	264
21a	41	SC (18)	Premenstrual	F	-	-	-	264
22a	46	SC (3)	Intermediate	F	96	72	++	264
23a	50	SC (12)	Intermediate	F	-	-	-	264
1a				G	-	-	-	264
2a				G	72	96	++	192
3a				G	?	?	?	240
4a				G	120	72	+	264
6a				G	96	144	+++	264
8a				G	120	48	++	264
9a	45	SC (10)	Atrophic	G	48	154	++	288
11a				G	72	144	+++	264
12a				G	120	48	+	240
14a				G	-	-	CCT	240
15a				G	-	-	-	216
16a				G	72	168	++++	264
18a				G	?	?	?	264
19a				G	-	-	-	336
21a				G	48	120	++	264
23a				G	144	48	+	264

(For footnote to Table I see opposite page.)

in doses of 4 mg. and each estradiol preparation in amounts of 1 mg. per injection. Estrone was used as an aqueous suspension only. Free estradiol was similarly employed, and also as a solution in propylene glycol and sesame oil, respectively. Estradiol dipropionate was prepared as a solution in sesame oil only; the benzoate was administered in menstrua of peanut oil and propylene glycol, respectively.

3. Daily vaginal smears were taken for a control period of approximately one week prior to therapy and for an average period of ten days thereafter. Approximately 900 smears were studied.

4. The average lag-time (hours between injection and vaginal response) for each preparation was as follows: estradiol dipropionate in sesame oil, 88; estradiol benzoate in peanut oil, 90; estradiol in aqueous suspension, 90; estrone in aqueous suspension, 100; estradiol in sesame oil, 108; estradiol in propylene glycol, 114; and estradiol benzoate in propylene glycol (one case), 120.

5. The average duration in hours of the vaginal response initiated by estradiol dipropionate in sesame oil was 100; by estradiol benzoate in peanut oil, 82; by estradiol in sesame oil, 36; by estradiol in propylene glycol, 120; by estradiol in aqueous suspension, 109; and by estrone in aqueous suspension, 110.

6. The degree of follicular activity varied widely with the preparation used and from subject to subject, but in any given instance, was directly proportional to the duration of the vaginal changes.

7. Climacteric patients reported symptomatic relief starting one to three days following injection and persisting for from three to ten days thereafter.

### Conclusions

About four to five days after the injection of 1.0 mg. estradiol, free or esterified, or its equivalent, 4.0 mg. estrone, regardless of menstruum, alterations in the vaginal secretion appear in the majority of nonmenstruating women. Under the conditions of our experiments, the time elapsed between the injection and the appearance of a change in the vaginal smear (lag-time) was approximately the same for each of the seven preparations employed.

The duration of the estrogenic response varied widely. The preparations producing the longest periods of follicular activity were estradiol in propylene glycol and in aqueous suspension and estrone in aqueous suspension.

The degree of stimulation of the vaginal mucosa varied considerably from subject to subject. The duration and degree of estrogenic response were directly correlated in any given individual but neither bore any demonstrable relationship to the specific preparation used.

The majority of climacteric patients reported symptomatic improvement, starting, on an average, one to three days after injection of the hormone and persisting for from three to ten days. The degree of relief of symptoms cannot be correlated with the objective findings in the vaginal mucous membrane.

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TABLE III. A COMPARISON OF THE EFFECTS OF ESTRONE AND ESTRADIOL IN EQUIVALENT DOSES UPON THE APPEARANCE, DURATION, AND HEIGHT OF THE VAGINAL RESPONSES OF 15 NONMENSTRUATING WOMEN

CASE NO.	AGE (YEARS)	THE VAGINAL RESPONSE					
		LAG-TIME (HOURS)		DURATION (HOURS)		DEGREE*	
		ESTRONE	ESTRADIOL	ESTRONE	ESTRADIOL	ESTRONE	ESTRADIOL
1a	54	-	-	-	-	CCT	-
2a	41	-	72	-	96	-	++
3a	46	?	?	?	?	?	?
4a	61	96	120	72	72	+	+
6a	48	-	96	-	144	-	+++
8a	41	96	120	120	48	++	++
11a	52	120	72	148	144	+++	+++
12a	52	168	120	84	48	++	+
14a	52	?	-	?	-	+++	CCT
15a	28	-	-	-	-	-	-
16a	33	96	72	152	168	+++	++++
18a	37	?	?	?	?	?	?
19a	28	120	-	72	-	+	-
21a	41	-	148	-	120	-	++
23a	50	-	144	-	48	-	+
Average	44	116	96	108	99	++	++

\*See footnote Table I.

Five women first injected with estrone, responded to both preparations. Two reacted more rapidly to estrone than to estradiol and 3 responded more promptly to estradiol than to estrone. In one instance, the duration of the changes in the vaginal smear was the same for each of the two injections, in three cases, it was longer following injection of estrone, and, in one instance, it was greater after the administration of estradiol. The degree of the response elicited by each of the two preparations was the same for three subjects. Estrone produced a greater amount of cornification of the vaginal epithelium than estradiol in one woman and the action of estradiol was more pronounced than that of estrone in one individual.

*Symptomatic Relief in Relation to Alterations in the Vaginal Smear.*—Most of the patients suffering from climacteric disturbances were among the groups of women who were tested with estrone and estradiol, respectively, in aqueous suspensions. The ability of estrogen to relieve symptoms without altering the vaginal smear has already been discussed at length in relation to the subjects of the present study.<sup>2</sup> Several points may be emphasized here. Symptomatic relief occurred prior to the appearance of the alterations observed in the vaginal mucosa, but the rapidity and degree of response were not quantitatively related to the changes later observed in the vaginal smears. In a number of instances, improvement in the general condition was acknowledged by the patient when objective changes were absent. The duration of symptomatic relief following administration of 1 mg. estradiol or an equivalent dose of estrone varied from three to ten days.

Summary

1. Forty-one women were treated with one or more injections of equivalent amounts of seven estrogenic preparations to a total of 57 tests. In thirty-nine tests, changes occurred in the vaginal mucosa; of these, however, seven were difficult to evaluate in relation to the administration of the estrogen. No objective response followed any of the remaining eighteen injections.
2. Free estrone, free estradiol, and the benzoic acid and dipropionic acid esters of the latter were the estrogens employed in these tests. Estrone was given

tion. This distinction is made very definite, and the statistics presented in the latter part of this report are taken from those patients who had surgery done for no other indication than the myomas. It is the practice in most clinics today, and rightfully so, I believe, to remove a myomatous uterus when major pelvic or vaginal surgery is undertaken for some other reason, even though the tumors are asymptomatic and might well be left undisturbed. Patients who had indications for surgery other than myomas will include many whose tumors were not causing, and would never have caused, trouble. There is a total, then, of 201 patients over 45 years of age who were operated upon solely because of uterine myomas.

TABLE I. MYOMAS AT UNIVERSITY HOSPITALS, CLEVELAND. JANUARY, 1942, THROUGH DECEMBER, 1946

Total patients of any age with myomas	1990
Patients over 45 years old with myomas	617
Patients over 45 treated by hysterectomy	408

TABLE II. DISTRIBUTION OF PATIENTS ACCORDING TO MENOPAUSE AND INDICATION FOR OPERATION

After the menopause	117 (28.7 per cent)		
Myomas the only reason for operation			42
Additional reasons for operation		75	
During the menopause	291 (71.3 per cent)		
Myomas the only reason for operation			159
Additional reasons for operation		132	
Totals	408	207	201

The fact that nonparous uteri are more likely to develop myomas than parous uteri is well known. On the basis of this, one would expect a higher proportion of the patients in this series to be nulliparous, than occurs in an unselected group of women of similar age, and such is the case, as is shown in Table III. Te Linde<sup>3</sup> quotes Hinselmann to the effect that approximately 20 per cent of women over 35 are nulliparous. Of the 408 patients studied here, 33.1 per cent were nulliparous, 29.8 per cent of those whose symptoms occurred during the menopause, and 41.1 per cent of those who had trouble after the menopause. In other words, one third of these patients were nulliparous, whereas only one fifth of the women over 45 in the general population have never had children.

The racial distribution of patients as determined in this series has little general significance. The proportion of Negro patients in this study is only about half of the proportion of that race in the University Hospitals of Cleveland's total census. A possible explanation for this may be the fact that myomas occur at an earlier average age in Negro women and grow to a larger size than they do in white women, and are therefore more frequently removed during the childbearing period.

The marital state of the patients studied agrees quite closely with that of the general population. Hinselmann<sup>3</sup> estimated that about 10 per cent of women over 35 have not been married, and these figures of 8.9 per cent and 11.1 per cent average to about 10 per cent.

On the basis of a series of 408 patients, then, we can conclude that marital status has no influence on the incidence of symptomatic myomas of the uterus after the age of 45, and that parity influences the development of symptoms indicating radical surgery only as it influences the incidence of myomas in general.

## MYOMAS DURING AND AFTER THE MENOPAUSE

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THE patient past the childbearing period who is found to have myomas of the uterus has long presented a problem. In 1891, J. T. Johnson,<sup>1</sup> of Washington, D. C., reported to the Southern Surgical and Gynecological Association that the "rule" stated in the textbooks—that uterine myomas cease to grow after the menopause—has many more exceptions than was generally supposed at the time. He recommended more frequent and earlier resort to radical operation in the treatment of these tumors in menopausal women. In the years since 1891, the continued growth of myomas after cessation of the menses, and the occurrence of cellular changes, such as benign degeneration and malignant change, have been so frequently associated, that there is at the present time considerable doubt that myomas ever increase in size after the menopause by simple growth. Whether his assumption concerning growth was right or wrong, Johnson did call attention to the fact that myomas can and do produce symptoms after the menopause.

The decision as to whether or not asymptomatic myomas should be left alone and watched, and as to how radical the treatment should be in the face of minor symptoms, is one to be made after consideration of the features of each individual case, and with a background of a knowledge of the behavior of these tumors during and after the menopause.

With a view to increasing this background of knowledge, a study was undertaken at the University Hospitals of Cleveland of all the hospital patients over 45 years of age having myomas of the uterus, in a five-year period from Jan. 1, 1942, through Dec. 31, 1946. Of these, the patients whose myomas were removed were studied in detail with regard to symptoms, preoperative diagnosis, the pathologic changes found, age, parity, menstrual history, and marital status.

Table I shows that there were 1,990 women with diagnosed myomas admitted to the hospital in the given five-year period. Of these, 617, or almost one third, were in or past the menopausal age group, and 408 (66.01 per cent) of them had hysterectomies performed because of their myomas.

In Table II, those 408 patients with which this report is concerned are broken down into the natural divisions of those who have definitely stopped menstruating, using three months or more of continuous amenorrhea as the criterion, and those who are still in the menopause. Approximately one fourth of the patients were postmenopausal. Each of these groups is then divided into patients on whom major surgery was performed for no other reason than a preoperative diagnosis of myomas, and those who had additional reasons for opera-

crease the size of the uterine cavity. The problem of why these tumors cause bleeding is still certainly far from solved, and the physiology of it presents an interesting challenge.

TABLE V. CHIEF SYMPTOMS WHEN MYOMAS WERE THE ONLY REASON FOR OPERATION

	BEFORE MENOPAUSE	AFTER MENOPAUSE
Bleeding	102	13
Pain	30	9
Growing mass	28	10
Backache	15	1
Urinary	5	2

The problem facing the clinician, however, is not why myomas cause bleeding but—are they causing the bleeding in the particular patient he is treating? Some light is thrown on this question by a comparison of the size of the tumor and the findings of the pathologist in the bleeding cases of this series. As shown in Table VI, one-fourth of the patients who were still menstruating showed, in addition to the myomas, other changes that could well account for the bleeding, and almost two-thirds of the postmenopausal patients showed such changes. Although this latter group is very small, and the figure of 61.5 per cent is not statistically important for this reason, I believe the proportion is so large that it has definite significance. Table VII shows the relative frequency of those associated conditions that could have been causing the bleeding, and it will be noted that they are all common to this period of life, and are all known to be the cause of uterine bleeding.

TABLE VI. DISTRIBUTION OF BLEEDING PATIENTS ACCORDING TO PATHOLOGIC EXPLANATION FOR BLEEDING

<i>During Menopause.—</i>	
Total patients	102
Patients with only myomas to explain bleeding	77 (75.5 per cent)
Patients with findings in addition to myomas to explain the bleeding	25 (24.5 per cent)
<i>After menopause.—</i>	
Total patients	13
Patients with only myomas to explain bleeding	5 (38.5 per cent)
Patients with findings in addition to myomas to explain the bleeding	8 (61.5 per cent)

TABLE VII. PATHOLOGIC FINDINGS OTHER THAN MYOMAS TO EXPLAIN BLEEDING

	DURING MENOPAUSE	AFTER MENOPAUSE
Endometrial polyp	12	4
Cervical polyp	5	
Atypical hyperplasia	4	2
Carcinoma of cervix	2	
Carcinoma of fundus	1	2
Chronic endometritis	1	
	25	8
All were undiagnosed before hysterectomy.		

The most interesting and probably the most instructive point brought out by this study is made by comparing the weight of the specimens with the pathologic findings, as is done in Table VIII. In women during the menopause whose uteri presented only myomas as an explanation for the bleeding, the average weight of the uterus and tumors was 501 Gm., whereas in those organs which also had polyps, atypical hyperplasia, or carcinoma to account for the bleeding, the average weight was only 288 Gm. A difference even more marked is

TABLE III. DISTRIBUTION OF PATIENTS ACCORDING TO PARITY, COLOR, AND MARITAL STATUS

	TOTAL	PAROUS	NULLIP.	COLORED	WHITE	MARRIED	SINGLE
During meno- pause	291	204 70.2%	87 29.8%	33 11.4%	258 88.6%	265 91.1%	26 8.9%
After menopause	117	69 58.9%	48 41.1%	28 24%	89 76%	104 88.9%	13 11.1%

The rest of this discussion is based entirely on those 201 patients who had no other indication for operation than myomas of the uterus. In other words, the tumors in these patients were considered by the surgeon to be causing enough symptoms or to be dangerous enough in themselves to warrant hysterectomy.

In gathering and calculating the statistics on this subject, there were two obvious factors that characteristically played a part in determining the decision to operate. As would be expected, these were size of the tumor, and the symptoms complained of by the patient. Of course, other factors are important, such as general health of the patient and mental attitude, but size and symptoms were the only two that could be compared statistically. In addition, there is a third factor, which did not lend itself to statistical comparison in this series, but which is equally important in the decision in favor of radical surgery. This is the increasing size of a tumor after the cessation of the menses.

Table IV shows the weight of the uterus and tumor from patients during and after the menopause. Roessle and Roulet<sup>4</sup> give the average weight of the normal uterus after the age of 45 as 50 Gm., with variations of 25 Gm. in either direction. Since preoperative estimation of the size and weight of the uterus and tumor must be based on palpation, it has been determined from the measurements and weights of surgical specimens that a uterus increased to the size of a 2½ months' pregnancy by myomas will weigh 450 to 500 Gm. The average size, then, of these 201 tumors was about the size of a two and one-half to three months' pregnancy. A few were within the normal limits of weight, but, as will be seen later, these uteri were the ones that had some other condition, undiagnosed preoperatively, which probably was causing the symptoms that led to operation.

TABLE IV. WEIGHT OF UTERUS AND TUMOR WHEN MYOMAS WERE THE ONLY REASON FOR OPERATION

	DURING MENOPAUSE	AFTER MENOPAUSE
Average weight	456 Gm.	542 Gm.
Extreme weights	75 and 2,890 Gm.	30 and 2,870 Gm.
Normal uterus	50 Gm.	50 Gm.

The most common symptom, as might be expected, was bleeding. A few of the patients presented two complaints that were considered equally important, so each was listed as an individual symptom in Table V. Those patients who are still menstruating present a particularly difficult problem in the evaluation of irregular bleeding. Many women have erratic periods and menorrhagia, and even metrorrhagia, during the last year or two of their menstruating life, without any pathologic change in the uterus. To say that a small or medium sized myoma that happens to be present at this time of life is the cause of the irregular bleeding, is an unjustified statement. It is difficult to imagine how subserous myomas or small intramural tumors can cause bleeding. Submucous nodules or larger intramural masses, and particularly pedunculated submucous tumors, do cause bleeding by alteration of the endometrial circulation, by necrosis and ulceration of the tumor mass, and perhaps by simple increase in the total amount of functioning endometrium, in the case of the very large myomas which in-



hysterectomy was performed because of myomas on five patients who had received deep x-ray therapy for myomas from one to twenty years previously.

Before concluding, it would be pertinent to determine what proportion of women over the age of 45 who have myomas of the uterus develop symptoms indicating surgical removal of the tumors. It is almost impossible to determine this accurately, but a rough approximation can be obtained. Crossen and Crossen<sup>2</sup> quote Kolb as having found that 50 per cent of all women over 50 have uterine myomas. On the basis of this and the approximately 20,000 admissions of women over 45 years old to University Hospitals of Cleveland during the five-year period studied, we can estimate that about 10,000 menopausal and postmenopausal women having myomatous uteri made up the field from which came the 408 patients studied in this series. In other words, approximately 4 out of 100 myomas cause serious trouble during or after the menopause.

### Summary and Conclusions

Four hundred eight women over 45 years of age with myomas of the uterus surgically removed were studied, with special attention to symptoms, size of tumor, and pathologic changes found. The marital status of the patient had no significance, and parity was significant only as it influenced the incidence of fibroids in general. Bleeding was the most common symptom, but only in the larger myomas (those above the size of a 2½ to 3 months' pregnancy) could the bleeding be consistently attributed to the tumors. With one-fourth to two-thirds of the smaller myomas, other causes for the bleeding were present, which were not diagnosed preoperatively. This is taken to indicate too hasty a decision in favor of hysterectomy and incomplete preoperative studies. Of the patients who noted increasing size of the tumor, all five had benign degenerative changes in the myomas, but no malignant changes were found.

In this series, approximately four out of 100 myomas in the general hospital population were troublesome enough to be considered an indication for hysterectomy. The average size of the tumors removed was about that of a 2½ to 3 months' pregnancy. It is believed that the above incidence of hysterectomies can be appreciably reduced by performance of thorough curettage before the final decision for hysterectomy is made in the instance of myomas smaller than a 2½ months' pregnancy, particularly in patients with bleeding as the chief symptom.

From the foregoing statistics and discussion, it is concluded that women approaching or in the menopause, who are found to have asymptomatic myomas smaller than a 2 months' pregnancy, may be carefully watched and given reasonable assurance that their tumors will probably not cause any trouble. The myomas larger than a 3 months' pregnancy are potentially troublesome, and, if the patient's general health and mental attitude are favorable, hysterectomy is indicated.

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seen after the menopause, where the respective weights were 643 and 227 Gm. In other words, small myomas are not likely to be the cause of bleeding, and when small myomas are found in the bleeding menopausal or postmenopausal patient, the surgeon is not justified in blaming the tumors, until he has eliminated such more likely possibilities as cervical and endometrial polyps, atypical hyperplasia of the endometrium, and fundal or cervical carcinoma. To put the figures differently for the patients past the menopause, of all the postmenopausal patients studied whose uteri weighed less than 500 Gm. (or were smaller than a three months' pregnancy), two-thirds of them had conditions other than the myomas to explain the bleeding.

TABLE VIII. WEIGHT OF UTERUS AND TUMOR CORRELATED WITH PATHOLOGIC FINDINGS IN BLEEDING PATIENTS

	DURING MENOPAUSE	AFTER MENOPAUSE
Myomas the only explanation for bleeding	501 Gm.	643 Gm.
Additional explanations present	288 Gm.	227 Gm.

Now, undoubtedly, some of these patients were best treated by hysterectomy, but it would seem that many of them would have been cured by a simple polypectomy or thorough curettage, and spared a laparotomy.

The one other symptom worthy of discussion is increasing size of a uterine tumor after the menopause. There were five patients in the postmenopausal group who presented this complaint. The myomas of each of these patients showed marked hyaline degeneration. In addition, edema was found in three, and cystic degeneration, focal hemorrhages, and calcification were each found in one of the tumors. There was no evidence of malignant change in any of them. All but one of the specimens weighed over 500 Gm., and the one that weighed less was noted to be increasing in size only by a physician.

When presented with an increasing tumor after the menopause, the physician naturally is concerned about malignant change. Frank,<sup>5</sup> in his textbook, makes a definite statement to the effect that myomas can not only continue to grow after the menopause, but may begin to develop after cessation of the menses, and quotes six different authors to support the statement. He does not clarify the word grow, but it is assumed that he means a natural growth, and not an increase in size due to an abnormal process. On the other hand, many recent texts maintain that myomas do not grow after the menopause except to increase in size because of degenerative processes or malignant change. Whichever statement is correct, the phenomenon of simple growth in uterine myomas after the menopause is at least rare, if it does occur, and any detectable increase in size warrants hysterectomy, on the probability that degenerative processes or malignant changes have been taking place. Of the five leiomyosarcomas of the uterus encountered in this series, all occurred before the cessation of regular menstruation. Four definitely originated in myomas, and the fifth was so extensive that the origin could not be determined. Only one of the specimens weighed less than 450 Gm.

There were seventeen patients, not included in this series, whose myomas were treated with radium or x-ray during the same five-year period. All but two were white private patients, and their ages ranged from 46 to 60 years. All but one had abnormal bleeding as their chief complaint, and the size of the myomas varied from one and one-half to four times that of a normal uterus. Eight patients had an associated atypical hyperplasia of the endometrium, which was considered an additional indication for the use of radiation therapy. Adequate follow-up information on these seventeen patients was not obtained in this study, but it is of interest to note that, in this same five-year period,

degrees of oliguria caused by dehydration. However, Ham and Landis<sup>7</sup> have reported that the urine and placentas of toxic patients do contain an antidiuretic substance which can be differentiated from the pituitary hormone.

In spite of all the negative and conflicting results, many writers still hold the hypothesis that pressor amines or "split proteins" are produced in ischemic areas of the placenta, and that these are the causative agents in eclampsia. Page<sup>12</sup> has marshalled a number of clinical observations consonant with the placental ischemia hypothesis. Relative ischemia of the placenta might be correlated with the increased incidence of toxemia seen in primiparous pregnancies, molar pregnancies, multiple pregnancies, polyhydramnios, placental infarction, cases of abnormal placentation, and in the hypothyroid, hypopituitary types of patients. It might also be related to intrapartum eclampsia and the rising frequency of toxemia as pregnancy approaches term.

We have taken up the general problem, utilizing a method which has vast possibilities in many fields. Lindbergh<sup>9</sup> has devised a perfusion apparatus in which one may keep organs or portions of organs alive for weeks. The conditions of the perfusion, oxygen supply, food supply, etc., may be varied at will. Here, then, is a means of experimental attack upon the question as to whether placental tissue produces the eclamptic toxin. This is a new approach, since the methods of extraction and autolysis remove either preformed substances or degradation products. Here we have an opportunity to investigate the production of substances by surviving or, if we elect, by dying placental tissue.

In the present paper, we shall describe a series of experiments in which we have extended the range of the so-far fruitless quest.

### Methods

Since absolute sterility is essential in the culture of organs, we have used only placentas from patients who were sectioned with unruptured membranes. An artery on the fetal side was cannulated, and glucosol was forced in by hand bulb, thus washing out the blood from the tissue supplied by the cannulated artery. A piece of washed-out tissue, weighing from 6 to 20 Gm. was then isolated and any "bleeders" were tied off. It was usually possible to take an entire cotyledon, which is an anatomical unit in that it is supplied by one artery and drained by one vein. The tissue was then put into the organ chamber of the pump, and the apparatus sealed and thoroughly "gassed" with a mixture of 80 per cent oxygen, 15 per cent nitrogen, and 5 per cent carbon dioxide. Perfusion was begun within an hour of the time that the placenta had been removed from the uterus. The initial perfusion medium was 300 ml. of 15 per cent human serum in Tyrode solution. At three-day intervals (usually), the tissue was changed to another pump and a fresh lot of perfusion medium used. Details of the variations will be indicated in reporting the results. All perfusions were done with a pressure of 96/54 mm. Hg in the organ. The pulsation rate was 90 per minute. The temperature of the system was 37° to 38°. In general, we adhered faithfully to the details of technique as outlined by Carrel and Lindbergh.<sup>1</sup>

In looking for a pressor substance in the perfusates, we used cats anesthetized with intraperitoneal sodium pentobarbital. A carotid artery was cannulated, and the blood pressure recorded on a smoked drum, using a mercury manometer. The perfusates, their concentrates, derivatives, etc., were injected into the femoral vein.

The assay for antidiuretic substance was carried out much as described by Teel and Reid,<sup>15</sup> using three to six rats for the assay of each preparation. The rats were gavaged with 0.2 per cent sodium chloride solution in quantities

## STUDIES ON SURVIVING HUMAN PLACENTAL TISSUE

### I. A Search for Pressor and Antidiuretic Factors

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THE placenta has long been favored as the culprit in hypotheses as to the cause of eclampsia. The most cogent evidence for this belief is the fact that hydatidiform mole, in the absence of a fetus, carries a high incidence of pre-eclampsia, and occasionally is accompanied by eclampsia. This association is particularly striking since the toxemia in molar pregnancy occurs at about the beginning of the second trimester, while, in pregnancies with fetuses, toxemia is rare before the third trimester.

At about the turn of the century, placental extracts, press juices, and autolysates were extensively investigated for the "elusive eclamptic toxin." Such preparations, given intravenously to animals, frequently caused convulsions and prompt death. For the most part, however, they were inactive when injected by other routes. Further investigation has shown that these immediate effects were usually either nonspecific anaphylactoid reactions, or were attributable to particulate blocking of the lung capillaries (Lichtenstein<sup>8</sup>). Oden,<sup>11</sup> Obata,<sup>10</sup> Dieckmann,<sup>5</sup> and more recently Schneider<sup>17</sup> have given intravenous injections of placental extracts presumably free of particulate matter, and produced quick death. According to Schneider,<sup>17</sup> this may depend upon intravascular clotting caused by placental thromboplastin.

Dixon and Taylor,<sup>6</sup> in 1908, reported that they had obtained a powerful pressor action in their placental extracts. However, the following year Rosenheim,<sup>16</sup> working in their laboratory, showed that the pressor activity was attributable to parahydroxyphenylethylamine and other bases formed by the action of putrefactive bacteria which had contaminated their preparations. Sterile placental extracts were without pressor activity.

More subtle factors than direct pressor agents have been sought in recent years. Dexter and Weiss,<sup>3</sup> after failure to find a pressor substance, could demonstrate no renin or reninlike enzymes in placental tissue. Page<sup>13</sup> could find no 1-dopa decarboxylase activity in placentas from normal or eclamptic pregnancies.

Many studies have been made of the histologic pathology, especially of the liver, following injections of placental preparations. These will be reviewed in a later paper, but it appears that no one using placental derivatives has produced a liver lesion generally accepted as reproducing the picture often, though not always, seen in human eclampsia, viz., fibrin thrombosis with focal peripheral hemorrhagic necrosis. Dieckmann<sup>4</sup> did obtain such a lesion in dogs by feeding meat in conjunction with the intraportal injection of "tissue fibrinogen" (thromboplastin). Since the placenta is rich in thromboplastin, this experiment may be significant.

Opinion is divided as to whether patients with toxemia excrete more anti-diuretic substance in the urine than do normal individuals with comparable

tion). None of the perfusates gave pressor responses. These perfusates were concentrated from two to ten times, depending upon the protein content.

Two experiments were done in which the perfusate was dialyzed for 24 hours against two changes of distilled water. In one, the unconcentrated perfusate was dialyzed, and in the other dialysis was done after concentration. Both the residual and the dialysate were then concentrated and assayed separately. No pressor response was found.

In another experiment, a branch of the cannulated artery was tied off, thus "infarcting" about one-half of the placental tissue. No pressor substance was found in the perfusate, nor could any be extracted from the dead portion.

All perfusates had their controls in perfusion medium saved from the lot put into the pump. The control media were concentrated, or dialyzed, incubated, etc., simultaneously with the test perfusates. All solutions were adjusted to pH 7.3 to 7.5 with carbon dioxide, before injection.

In sum, we have not been able to find a condition under which surviving placental tissue produces a detectable amount of a pressor substance. There are, of course, many variables which have not been tried, or even thought of—but that is the difficulty with negative results.

TABLE I. THE EFFECT OF PLACENTAL PERFUSATES UPON DIURESIS IN RATS\*

CONDITIONS OF PERFUSION	CONTROLS			TEST		
	NO. OF RATS	PERCENTAGE OF WATER LOAD EXCRETED IN 3 HOURS		NO. OF RATS	PERCENTAGE OF WATER LOAD EXCRETED IN 3 HOURS	
		MEAN	RANGE		MEAN	RANGE
Rapid, 3 days	3	54.4	54-55	3	53.9	45-59
Rapid, 6 days	6	48.2	36-62	6	55.1	41-80
Rapid, 4 days	4	54.9	51-59	4	29.4	12-51
Rapid, 4 days	6	41.2	30-48	6	40.1	20-76
Rapid, 3 days	5	54.0	40-80	6	45.0	16-79
Slow, 1 day	4	44.5	25-65	6	29.3	19-40
Slow, 1 day	3	55.2	35-81	5	25.3	0-56
Slow, 2 days	6	38.2	26-53	5	31.7	16-41
Slow, 2 days	6	54.7	43-73	6	22.8	1-41
Slow, 2 days	5	72.0	57-83	5	55.5	44-71

\*All placentas from normal patients. All perfusions done in 80 per cent oxygen. All perfusates concentrated ten times in a vacuum desiccator at room temperature.

*Antidiuresis.*—About half of the placental perfusates assayed have shown an antidiuretic effect when concentrated ten times and injected subcutaneously into rats. With one exception, the active perfusates have come from experiments in which the placenta was purposely perfused very slowly, i. e., under conditions of artificial "ischemia." Also, with one exception, the assayed perfusates of all placentas so perfused have shown antidiuretic activity. We do not have enough experiments to determine whether this slow perfusion is the controlling factor. The results of all experiments are shown in Table I, and in Fig. 1. The findings in all rats injected with the "ischemic" perfusates are depicted in Fig. 2. The spread of the distribution curves, as in most bio-assays, is most distressing to one who likes to base conclusions on clear-cut differences. However, 63 per cent of the test rats excreted less than 40 per cent of the water load, while only 17 per cent of the animals injected with the control concentrate failed to excrete more than 40 per cent of the load.

*Chloruresis.*—Whether the pituitary antidiuretic hormone has a chloruretic effect is still *sub judice*, although most workers have thought that it has. Ham and Landis<sup>7</sup> have shown that the urinary excretion of chlorides increases steadily as the dose of Pituitrin is increased over a 1,000 fold range. They state that

equivalent to 5 per cent of the body weights. When diuresis was well established, about 80 minutes later, a second gavage equal to three per cent of the body weight was given, and 1 ml. of the placental perfusate was injected subcutaneously. The urine output of each rat was then determined over a three-hour period. The three-hour output was calculated in terms of percentage of the water load (load= sum of gavages plus 1 ml. of injected perfusate minus urine volume output during the establishment of diuresis).

In the experiments to be reported here, the placental perfusates, and their controls, were concentrated ten times in a vacuum desiccator at room temperature. The controls were portions of the perfusion media which had been withheld when the experiments were started.

The urinary chlorides were determined by the method of Volhard and Harvey.<sup>14</sup>

### Results

*Survival of the Tissue.*—In all, more than 75 successful placental cultures have been made. Pieces of placenta have been kept in good condition for as long as four weeks. At the end of the experiments, the tissue looked normal grossly and histologically, and was still producing gonadotrophic hormone. The tissues perfused throughout with only 15 per cent serum showed nuclei which did not stain with normal intensity. During some of the experiments, the tissue had withstood periods of anoxia with no apparent damage. Near the end of some experiments, undiluted plasma from the blood bank was used. The tissues seemed to oxidize citrate rapidly, as evidenced by considerable rises in the pH of the perfusate (citrate ion oxidized, leaving sodium to combine with water and carbon dioxide to form sodium bicarbonate).

*Failure to Find Pressor Activity.*—The only effect ever found upon the blood pressure, following intravenous injection of the perfusates or their derivatives, was an occasional drop. Usually and characteristically the blood pressure remained constant within 10 mm. Hg.

The general plan of procedure was to perfuse the placental tissue for three days under the conditions described above. The placenta was then transferred to another pump and perfused for three or four days anoxically. The gas phase in this variation was 95 per cent nitrogen and 5 per cent carbon dioxide. Following the anoxic perfusion, the placenta was again transferred to another pump with fresh medium, and again perfused in oxygen. After three days, another variation was tried. Total periods of perfusion ranged from 11 to 28 days. Some experiments were done in which the perfusion rate was greatly reduced, and the tissue was presumably dying; here, the period of perfusion was 24 hours.

In the first experiments, the original perfusates were assayed; the volume of injection was from 20 to 50 ml. Since these elicited no pressor responses, the whole volume of perfusate (250 to 275 ml. recovered from the pump) was concentrated ten times in a vacuum desiccator at room temperature. Twenty ml. of the concentrate, or 2/3 of the entire volume of perfusate, failed to elicit any pressor response. The anoxic perfusates never increased the blood pressure, and in about one third of the cases caused rather marked drops in pressure.

In the first three experiments, the perfusion medium consisted of 15 per cent serum and 85 per cent Tyrode solution. Since so dilute a serum might not contain enough of a hypothetical precursor for the placenta to make a pressor substance, later experiments were made with varying concentrations of serum or citrated plasma. The maximal serum concentration used was 70 per cent, and the maximal plasma concentration was "undiluted" bank plasma (which actually is about 80 per cent plasma and 20 per cent citrate and dextrose solu-

this is in agreement with a prediction made by Silvette that Pituitrin might be assayed more accurately by its chloruretic effect than by its antidiuretic activity. Several other workers, however, have attributed the chloruresis to the Pitocin contaminating the Pituitrin preparations. According to Smith,<sup>18</sup> the Pitocin effect may be referable to changes in the rate of glomerular filtration rather than to a specific effect upon the renal tubular reabsorption.

Since some of our perfusates seemed to be definitely antidiuretic, we have determined the chloride excretion in the same experiments. As Fig. 3 shows, no chloruretic effect was ever observed. There was no increase in either the total excretion or the urinary concentration of chloride in any experiment. This, perhaps, accords with the finding of Ham and Landis<sup>7</sup> that there is no chloruretic activity associated with the antidiuretic substance extracted from placentas of patients with toxemia of pregnancy.

### Discussion

Our assays for a pressor substance have obviously been acute experiments. They have ruled out the presence of a direct pressor agent in our perfusates, and thus speak against the hypotheses built around the production of pressor amines in the placenta. We have not determined whether these placental perfusates can cause hypertension secondarily and through the intermediation of some other agent.

In view of the negative results in the search for a pressor activity in our perfusates, the question rises as to whether we used enough placental tissue. A rough calculation seems to indicate that we did. The average weight of placental tissue perfused was about 15 Gm. The volume of concentrated perfusate injected in the pressor assays represented two thirds of the total perfusate, and would therefore be equivalent to the three-day metabolite production of 10 Gm. of placenta. The assays were made with cats weighing about 2 kg. In proportion, this would be equivalent to 300 Gm. of placenta producing metabolites for three days in a 60 kg. woman.

The experiments do not rule out the possibility that the placenta does produce a pressor substance. We have perfused the fetal vessels, and it is conceivable that substances of high molecular weight might not pass from the maternal constituent of the placenta into the fetal circulation. Clinically, pre-eclampsia usually does not occur in the fetus of the toxic mother; the baby's blood pressure is normal.<sup>3</sup>

It is interesting that antidiuretic activity in the placental perfusates was usually associated with slow "ischemic" perfusion of the tissue. Ham and Landis<sup>7</sup> found an antidiuretic activity in the extracts of placentas from patients with toxemia, but not from normal patients. No conclusion can be drawn as to the relation between these two observations, but it is worth pointing out that our placental perfusion experiments were undertaken on the hypothesis that inadequate perfusion might imitate what happens in the placenta of a patient developing toxemia.

In a review of the literature, Chesley<sup>2</sup> concluded that the cause of edema formation in incipient pre-eclampsia is unknown, since none of the physical factors studied could be incriminated as the primary cause. It is possible that

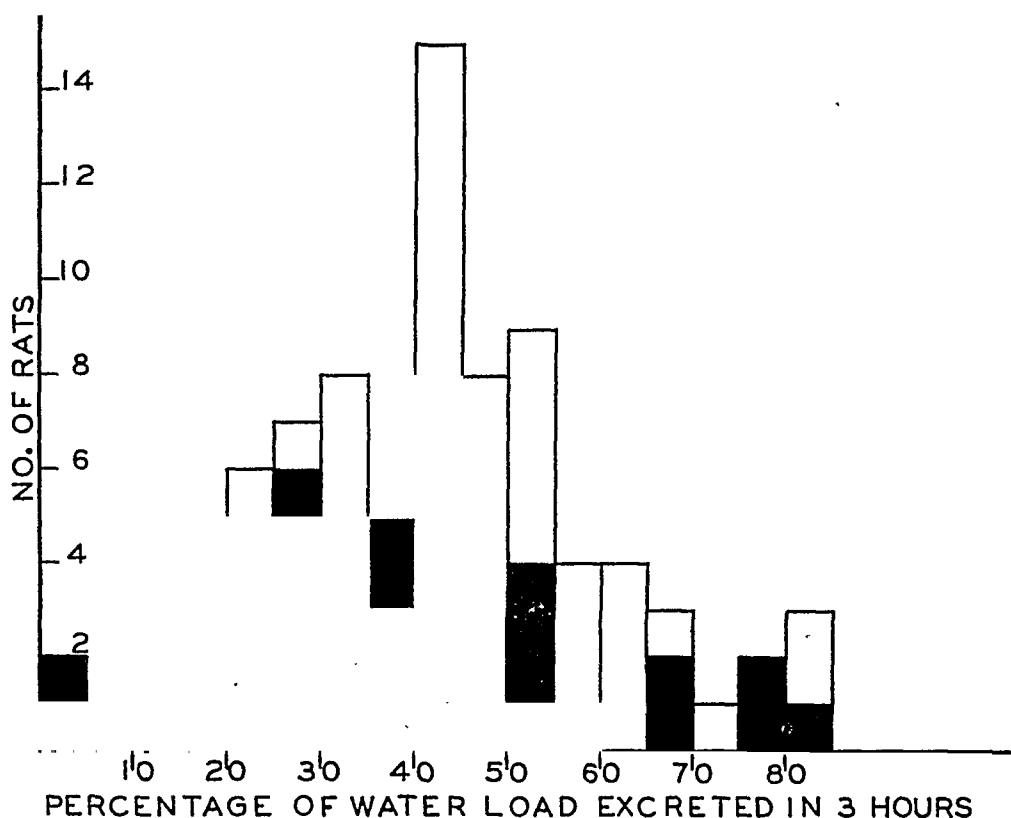


Fig. 1.—Diuresis in individual rats, as percentage excretion of the water load in three hours.

□ Control  
■ Test

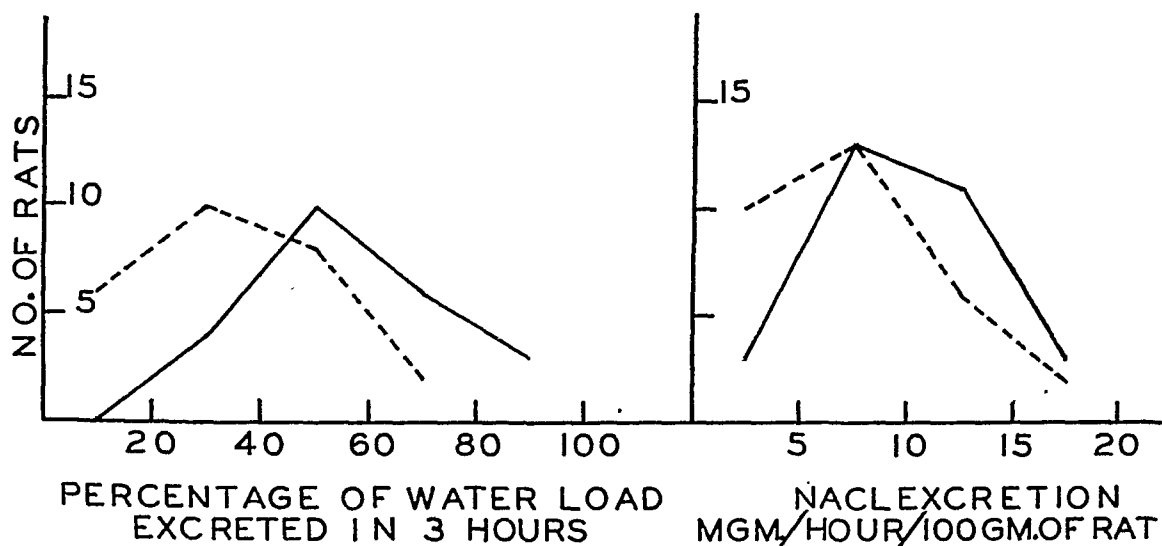


Fig. 2.

Fig. 2.—Frequency distributions of diuretic response in rats injected with perfusates from "ischemic" perfusions (broken line), and their controls (unbroken line).

Fig. 3.—Frequency distributions of chloride excretion in the rats represented in Fig. 2. Unbroken line: Control. Broken line; Test.

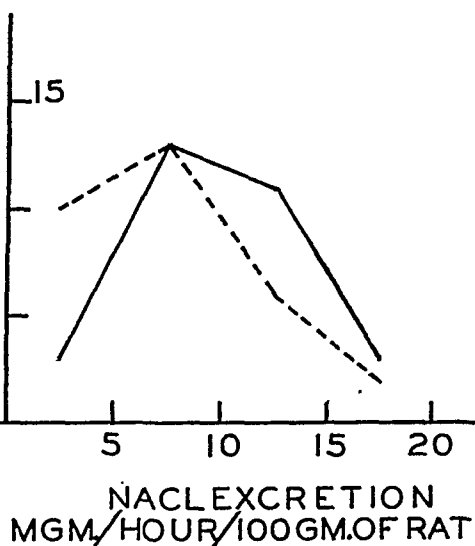


Fig. 3.



## CLINICAL EVALUATION OF SULFAMERAZINE IN POSTPARTAL AND POSTABORTAL SEPSIS\*

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THE purpose of this paper is to report the results of treatment of eighty-eight cases of postpartal and postabortal sepsis using sulfamerazine.

Sulfamerazine, the monomethyl derivative of sulfadiazine, is 2-sulfanilamide-4-methylpyrimidine, and was synthesized at about the same time as sulfadiazine by Roblin and his coworkers<sup>1, 2</sup> and by Sprague and his associates.<sup>3</sup> Preliminary studies<sup>1, 2, 3</sup> indicated that this derivative had promising chemotherapeutic activity, but it received little attention until recently when attempts were made to find a more satisfactory sulfonamide.

Pharmacological and clinical studies of sulfamerazine administered orally,<sup>4-13</sup> have shown that a higher concentration in the blood is attained more rapidly and maintained longer than that attained by equal doses of the more commonly used sulfonamides. These characteristics result from its rapid and more complete absorption from the gastrointestinal tract, and its slower excretion by the kidneys. Careful clinical and experimental investigations have been made on the solubility, absorption, excretion, and toxicity of sulfamerazine.

Welch, Mattis, Latven, Benson, and Shiels<sup>13</sup> showed that more sulfadiazine than sulfamerazine was excreted in the urine in the first twenty-four hours despite the fact that the blood reaching the kidney was much lower in its sulfadiazine content. They then anticipated that with equivalent blood concentrations of the two drugs, with a slower renal excretion of sulfamerazine, a definitely lower concentration of that drug should occur in the urine at any given time. This, plus the greater solubility of the free and acetylated forms of sulfamerazine in neutral or acid urine, in comparison with the sulfadiazine, offers additional protection to the urinary tract from crystallization. Others<sup>4, 6, 7, 10, 11, 14, 15, 16, 17</sup> have found sulfamerazine to be more soluble in acid urine than sulfadiazine and hence more desirable from the standpoint of less renal toxicity.

Various workers<sup>4, 6, 7, 9, 11, 13, 14</sup> have demonstrated in both experimental animals and man that higher blood levels are obtained more rapidly and maintained longer with sulfamerazine than with the more commonly used sulfonamides. Likewise, it has been observed that this drug is removed from the blood stream more slowly than similar preparations. Sulfamerazine also produces a higher concentration in the blood with a smaller dose than sulfadiazine.<sup>4, 6, 10, 11, 12, 13</sup> Thus, less frequent doses of the drug are necessary to maintain an adequate blood concentration.<sup>9, 10, 11, 13</sup> The rapidity of absorption suggests that intravenous injection may not be necessary when it is desired to produce an adequate blood concentration quickly.<sup>4, 6, 13</sup>

\*The sulfamerazine used in this study and funds for this study were supplied by Sharp & Dohme, Inc.

the placental antidiuretic substance plays a role in the accumulation of water in these toxic patients, but we cannot assess its importance. Edema is not pre-eclampsia.

### Summary and Conclusions

Human placental cotyledons were kept alive in Lindbergh pumps and perfused under varying conditions of oxygen supply, perfusion rate, protein content of medium, etc.

None of the perfusates showed any pressor activity.

Perfusates from placentas artificially "ischemic" usually had some anti-diuretic activity, while those from placentas perfused more adequately usually had no such activity.

The antidiuretic perfusates had no effect upon the urinary excretion of chlorides.

We wish to acknowledge our indebtedness to Herbert S. Gasser, Edric B. Smith, and John Campo of the Rockefeller Institute, for the loan of the Lindbergh-Carrel apparatus.

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alone. Two of the eighty-eight cases did not respond to sulfamerazine after five days and continued to run a low-grade fever, but did become afebrile when sulfadiazine was substituted.

The majority of the blood cultures were reported negative but there were eight cases of *Staphylococcus albus*, one of *Staphylococcus aureus pyogens*, and three of *Staphylococcus albus hemolyticus* reported. However, in view of the clinical course of the corresponding patients, these positive cultures are believed to be the result of contamination. Likewise, urinary findings were essentially negative on the majority of cases reported, unless a pyelitis was associated with the endometritis. Gram-negative bacilli were the usual offending organism in such cases.

The total dosage of sulfamerazine varied from 6.5 Gm. given over a two-day period in a case of postpartal endometritis to 40 Gm. given over an eleven-day period to a patient with a septic abortion with pelvic thrombophlebitis and pulmonary infarction. However, in the majority of cases, the average total dose of the drug was about 12 to 16 Gm. given over a three- to four-day period. The concentration of free sulfamerazine in the blood, obtained as previously described, varied markedly in eleven patients treated with 1 Gm. initially and 0.5 Gm. every four hours, from a low level of 0.92 mg./100 c.c. on a sample obtained two hours after the second dose of the drug to a high of 12.4 mg./100 c.c. on the fourth day of treatment. The average blood concentration was about 5 mg./100 c.c. in the majority of cases. In the remainder of the cases, giving 3 Gm. of the drug as the initial dose and 1 Gm. every six hours, the blood concentrations varied from a low of 0 mg./100 c.c. three hours after the initial dose to a high of 21 mg./100 c.c. on the fourth day of therapy. On this regime, the blood concentrations were so variable between individual patients that one cannot state a definite concentration that would be accurate or would apply to the different cases. It was noted that some patients consistently had a high level of free sulfamerazine in the blood, whereas other patients whose blood was drawn and analyzed at the same time constantly had a much lower concentration of the drug in the blood. However, the clinical response to treatment was the same in both types of cases. This marked variability in concentration may be explained partially on the individual ability of the patient to absorb the drug and the amount of urine excreted daily. Too, the administration of sodium bicarbonate to alkalinize the urine results in the relative inhibition of the reabsorption of sulfamerazine by the renal tubules and consequent lowering of the plasma concentration of sulfamerazine. It is also known that, in some cases, the individual being treated did not take any or took only a portion of each dose of the drug which would further tend to confuse the results. An attempt to correlate the intake and output with the concentrations obtained was unsuccessful. Some cases showing a high daily intake and output had a high concentration of the drug in the blood, whereas others on a much lower intake with a lower output had low concentrations.

In this series of cases, twenty-seven of the patients received no sodium bicarbonate or potassium citrate with the sulfamerazine to alkalize the urine. It is worthy of note that no toxic reactions as manifested by hematuria, loin pain, psychosis, leucopenia, nausea and vomiting, or dermatitis were encountered, with or without alkalization, in this study. Only one patient could be considered to have had toxic symptoms from the drug, and that consisted of a low-grade fever which subsided when the drug was discontinued.

Thus, in résumé, we find sulfamerazine to be an effective, practically non-toxic sulfonamide in the treatment of postabortal and puerperal sepsis. High blood concentrations of the drug are attained more readily and maintained longer with less of the drug than with the more commonly used sulfonamides.

Extensive work has been done on the relative toxicity of sulfamerazine. Some of these observations were from the clinical use of the drug in treatment of various infections,<sup>4, 5, 6, 8, 9, 10, 12, 15, 18</sup> and others were the direct results of laboratory experiments on animals.<sup>13, 14</sup> In general, the observers concluded that sulfamerazine showed a low incidence of toxic manifestations. It was no more toxic than the commonly used sulfonamides<sup>4, 5, 6, 9, 10, 12, 13, 19</sup> and probably more desirable in so far as solubility and renal toxicity were concerned.<sup>14</sup> Sulfamerazine has further been studied with respect to its antibacterial activity. Experimental observations<sup>1, 2, 20, 21</sup> on various animals and in vitro have shown sulfamerazine to be quite effective in the treatment of pneumococcal septicemia, meningitis, staphylococcal and streptococcal infections. The drug has been used clinically with good results in the treatment of pneumococcal pneumonia, meningococcal meningitis, erysipelas, streptococcal infections, gonococcal urethritis, nonspecific urinary tract infections, and colon bacillus infections.<sup>5, 6, 8, 9, 10, 12, 15, 18</sup> The general conclusions are that in the majority of cases sulfamerazine is equally as effective a therapeutic agent as sulfadiazine.

### Present Study

The present study was conducted on postpartal and postabortal septic cases on the Tulane Obstetrics and Gynecology Service at Charity Hospital of Louisiana at New Orleans. The majority of the cases consisted of postpartal patients who were considered septic if they had a temperature of 100.4° F. for two consecutive days. However, in a few there was gross evidence of infection on admission and chemotherapy was started immediately. Likewise, a few cases were treated prophylactically because of low-grade fever and a foul lochia post partum.

Of the eighty-eight patients followed who were treated with sulfamerazine, there were sixty-seven cases of postpartal endometritis; four of acute endometritis from septic incomplete abortions; three of puerperal morbidity, cause undetermined; two of endometritis and parametritis; three of postpartal pyelitis; three of pyelitis and endometritis; one of postpartal sepsis following intrapartum sepsis from prolonged rupture of the membranes; one septic criminal abortion with pelvic thrombophlebitis and pulmonary infarction; one of endometritis and suppurative thrombophlebitis of the pelvic veins; one of endometritis from an incomplete septic abortion with retained placenta; one of endometritis from prolonged ruptured membranes with thrombophlebitis of the superficial internal saphenous vein; and one of pelvic thrombophlebitis.

At the beginning of this study, the initial dosage of sulfamerazine was 1 Gm. orally, followed by 0.5 Gm. every four hours, day and night, with an equal dose of sodium bicarbonate or potassium citrate. Later the dosage was changed to an initial dose of 3 Gm. orally and 1 Gm. every six hours, day and night, with equal doses of sodium bicarbonate or potassium citrate. Toward the last of the series the sodium bicarbonate or potassium citrate was discontinued altogether. With the smaller dosage of sulfamerazine, blood samples were taken about midway between the second and third dose of the drug, and with the larger dosage a blood sample was obtained three hours after the initial dose. Using the method of Bratton and Marshall,<sup>22</sup> the concentration of free sulfamerazine in whole blood was determined on the sample obtained and then every twenty-four hours for the first two days and every other day thereafter. A record was kept of the temperature at the time of drawing the blood sample, the highest temperature reading of the day, and the daily intake and output. Blood cultures were taken on all cases prior to administration of the drug.

Combined penicillin and sulfamerazine therapy was used in thirteen of the eighty-eight cases. These were patients who were either very septic on admission or whose septic course did not respond readily to sulfamerazine therapy

Seven years later (1946) the patient became pregnant and delivered a full-term normal infant. In January, 1948, she delivered another full-term normal infant. To date there has been no clinical evidence of breast cancer and the patient is in apparent good health.

CASE 4.—Mrs. H., white, aged 27 years, was admitted to hospital in December, 1938. Chief complaint: lump in the right breast.

Several weeks previous to admission, the patient had first noticed a lump in her right breast which, in the past month, had increased in size until it was the size of a plum. She had had one pregnancy ten years previous to admission. Two years prior to admission, a simple cyst had been removed from her left breast.

Examination revealed a young, well-developed woman. Right breast, showed a lump about 4 by 4 by 3 cm. in the outer upper quadrant, freely movable, not tender, but of indefinite outline; not attached to skin or structures beneath the mass. Left breast—no tenderness or masses. Small 1½ inch scar present below nipple.

On Dec. 4, 1938, a frozen section showed malignancy and a radical breast amputation was done.

Pathological examination showed: a mass 6 by 6 by 4 cm. present in the breast tissue, not encapsulated. An area at the periphery showed adenocarcinoma; the other areas showed fibrous tissue; dilated ductules. Axillary lymph nodes showed acute hyperplasia—no sign of metastases. Diagnosis: Adenocarcinoma of right breast.

Six years later, in 1944, the patient became pregnant and delivered a normal full-term infant without complications. She was examined in 1947, showed no clinical evidence of metastases, and was in apparent good health.

Of the four cases presented, three are now free from symptoms and metastases. The important factors common to the three cases are:

1. A radical mastectomy for carcinoma was done.
2. There was no involvement of the axillary nodes at operation.
3. Pregnancy followed radical breast amputation.
4. There was a time interval between surgery and pregnancy of more than five years.

In the fourth case, where metastatic involvement occurred, the tumor had a greater degree of malignancy, the time interval between surgery and subsequent pregnancy was relatively short, and the clinical course was progressively bad.

In reviewing the literature as to the question of pregnancy following radical mastectomy for carcinoma of the breast, a marked difference of opinion is found. Rosenthal,<sup>14</sup> Weibel, Redwitz,<sup>19</sup> Reidel, and others believe that pregnancy will activate any cancer growth present and hasten the fatal outcome.

Bromeis<sup>2</sup> and Nölle<sup>10</sup> have found that pregnancy following radical mastectomy does not as a rule lead to local recurrence of the lesion, but that there is a greater danger of formation of a new, primary cancer in the other breast. Gusnar<sup>18</sup> found this true and added the opinion that if the patient had had a previous pregnancy in conjunction with carcinoma of the breast, there was a greater tendency to local recurrences as well as a greater incidence of a second primary lesion in the other breast.

The three cases substantiate Harrington's<sup>5</sup> conclusions based on his series of 4,682 cancers of the breast, in which 55 patients who had been operated upon for carcinoma of the breast subsequently became pregnant. He found that patients who have been operated upon for malignant disease of the breast can

the chest wall or skin and was freely movable. The mass was tender and on palpation a dark brownish fluid exuded from the nipple.

On March 17, 1935, a radical mastectomy was done.

Pathological examination showed: "Villous duct adenocarcinoma confined to the mass near the nipple. Remainder of breast tissue showed some dilatation of ducts. Axillary tissue showed no evidence of malignancy."

The patient's convalescence was uneventful and she was discharged on March 26, 1935.

Five years later (1940) she was seen, now in her third month of pregnancy. Her prenatal course was uneventful and she delivered spontaneously. She was again seen in 1948 and is in apparent good health.

CASE 2.—Mrs. C., white, aged 28 years, was admitted to hospital April 3, 1944.

Chief complaint: small nodule in left breast.

The patient noticed a small nodule in the outer quadrant of her left breast four days previous to admission. Nodule removed, size 4 by 3 by 2 cm.

Pathological examination showed: "Benign fibroadenoma."

Patient discharged April 4, 1944. Within thirteen months the patient noticed a small nodule in the scar line and returned to her surgeon. She was re-admitted to hospital May 22, 1945, and a semiradical amputation of the left breast was done.

Pathological examination showed: "Adenocarcinoma." Five glands taken from fatty tissue and edge of muscle ranging from 0.5 to 1 cm. in diameter showed metastatic evidence of adenocarcinoma.

Patient discharged June 2, 1945, and was then given a full course of deep x-ray therapy. She was examined in March, 1946, at which time there was no clinical evidence of recurrence of the malignancy. In January, 1947, the patient was again seen and was about two months pregnant and the estimated due date was Aug. 30, 1947. There was no evidence of metastases at this time. Her pregnancy was uneventful until six weeks before the expected date of confinement. At that time she began to complain of sacroiliac discomfort and limped slightly with her left leg. X-rays of the pelvis early in August revealed no bone metastases. Patient delivered a full-term infant in late August. Post partum she continued to complain of sacroiliac pain and a marked secondary anemia persisted despite antianemia therapy. Her symptoms persisted and she was admitted to the hospital in October. X-ray revealed metastases to left hip, back, and skull. The patient expired in December with metastatic carcinoma of the lungs.

CASE 3.—Mrs. T., white, aged 23 years, was admitted to hospital April 2, 1939.

Chief complaint: lump in left breast.

The patient first noticed a tender lump in her left breast two weeks previous to admission. The lump had not changed in size as far as she knew.

Examination revealed a well-developed young woman. Right breast—normal. Left breast—showed the presence of a small lump the size of a marble in the outer upper quadrant, freely movable, not tender.

The tumor was excised.

Pathological examination showed: ovoid mass of tissue measuring 26 by 20 by 15 mm. In the central portion of the tissue there was a firm mass which at one point had a tendency to irregular infiltration of the tissue. Diagnosis: Hyperplastic adenoma with malignant degeneration.

The patient refused further surgical treatment but had eighteen deep x-ray treatments immediately following operation. She was re-admitted June 26, 1939, with the complaint of a hardened area in the right lower part of the left breast below the previous scar. A radical mastectomy was performed.

Pathological examination showed: "Chronic mastitis with lymphocystic and plasma-cell infiltration. Benign fibrous involution. No evidence of malignancy."

## CYLINDROMA OF THE CERVIX WITH PROCIDENTIA

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COMPLETE prolapse of the uterus complicated by carcinoma of the cervix is an uncommon condition. In 1943, Harvey and Ritchie<sup>7</sup> reported finding only 78 cases in the English literature. We are reporting a case of complete prolapse in which the cervix contained a squamous-cell carcinoma, Grade 3, in situ, associated with an infiltrating adenocarcinoma (cylindroma type). We were unable to find any other recorded case of cylindroma of the cervix in the literature.

Bauer and Fox<sup>1</sup> credited Billroth with coining the term "cylindroma" in 1856, to refer to the peculiar stroma of the tumor. Cylindromas are seen most commonly in the salivary glands, and comprise 15 to 20 per cent of the tumors of these glands.<sup>3</sup> There is no way of differentiating cylindromas from mixed tumors of the salivary glands on gross examination. The microscopic picture, however, is characteristic. There are plugs or cylinders of small hyperchromatic tumor cells in a fibrous or hyaline stroma. The plugs are often "honeycombed," and these central spaces may contain mucus or hyaline substance which represents attempts at acinar formation. At the periphery the plugs often show some degree of palisading of the nuclei. Infiltration of nerves is a characteristic feature of many of these tumors. According to Quattlebaum, Dockerty, and Mayo,<sup>9</sup> cylindromas of the salivary glands have a marked tendency to recur and metastasize, and the prognosis for patients who have this lesion is poor. Cylindromas elsewhere, however, are more benign in nature. Steinmann<sup>10</sup> recorded four cases of cylindroma of the ethmoid region and stated that cylindromas are benign, but frequently recur locally. Bauer and Fox reported three cases of this tumor in the palatal mucous glands, and stated that they are benign but may become cancerous. McDonald<sup>8</sup> reported cylindromas of the trachea and bronchus as a type of slowly growing adenocarcinoma. Fossel<sup>5</sup> reported one case of cylindroma of the vulva in which cure followed local excision.

### Report of Case

A white woman, aged 67 years, came to the Mayo Clinic April 20, 1948, because of vaginal bleeding which she had had for one month. Two siblings had died of carcinoma of the stomach.

The patient had had typhoid fever and malaria at 10 years of age. Her two pregnancies went to term. In 1903, at 22 years of age, bilateral oophorectomy had been done for diseased ovaries. This was followed by cessation of menses and menopausal symptoms. For thirty years the uterus had prolapsed outside the vagina but otherwise she was well until one month prior to entry to the clinic. At that time she had noticed the onset of vaginal bleeding. The blood was bright red; bleeding occurred intermittently and varied from slight to profuse.

Physical examination revealed a well-developed and well-nourished woman. General examination gave negative results except for blood pressure of 160/90. Pelvic examination revealed complete prolapse of the uterus associated with cystocele, Grade 4, and rectocele, Grade

survive a full-term pregnancy for a number of years without recurrence of cancer, and that the number of years of apparent freedom depend on the malignancy of the lesion, the degree of axillary involvement, and the time interval between surgery and subsequent pregnancy.

### Conclusions

1. A more favorable prognosis may be given to patients who have had radical surgery of breast for cancer and have subsequently become pregnant after an interval of five or more years.

2. Where there was metastatic spread to the axillary nodes before surgery was done and where there was a subsequent pregnancy in less than four years, the clinical course was progressively downhill.

3. In the four cases presented, there was no evidence of a greater tendency for a new primary cancer in the other breast to develop.

4. Patients adequately treated for early carcinoma of the breast and not having a subsequent pregnancy for four or more years may have apparent freedom from recurrence of the cancer and symptoms for five or more years.

These conclusions suggest the basis for treatment in the type of case presented. More definite conclusions cannot be stated, not only because of the small series of cases presented but because three out of the four cases had all the advantages for a most favorable prognosis. It is hoped, however, that the information given will be of help to those who are confronted with the management of similar cases.

We wish to acknowledge our gratitude to the following people for their help in compiling this paper: Drs. Ashton, Hober, LaSalvia, Nelson, Peltz, Sturgis, and Miss Rathgen.

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gynecologists and general surgeons in the United States. Of these, 28 (58.3 per cent) had never seen a case, 11 had seen one case and 9 had seen two or more cases. Judd's<sup>6</sup> reply to this questionnaire stated that he had found three cases among 2,188 cases of procidentia of the uterus at the Mayo Clinic, an incidence

Fig. 2.

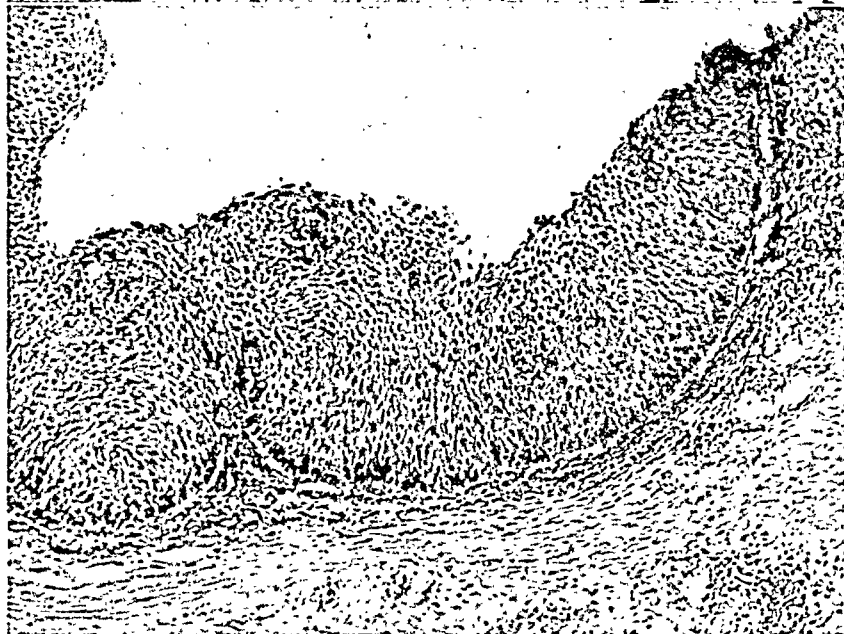
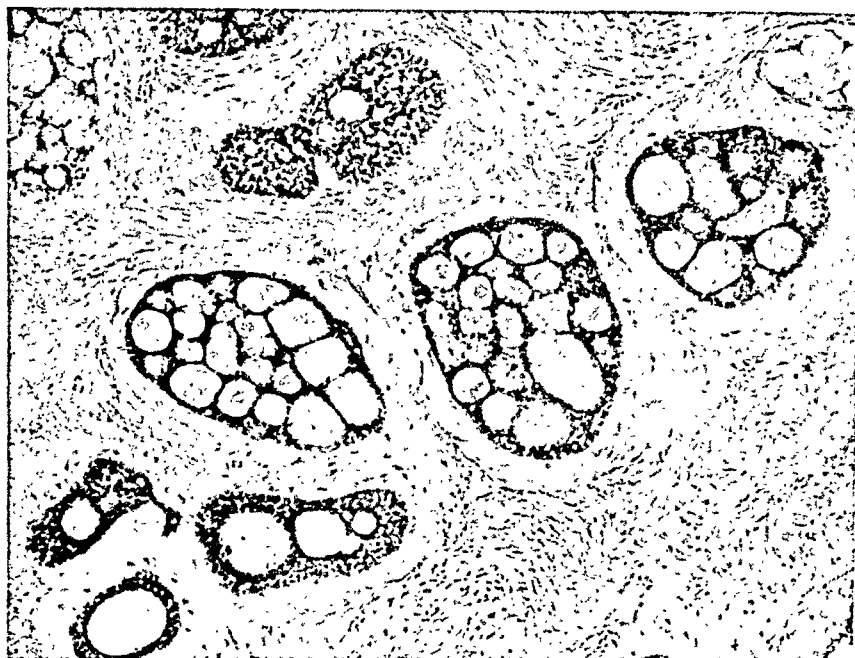


Fig. 3.

Fig. 2.—Microscopic pattern of the cylindroma (hematoxylin and eosin,  $\times 100$ ).

Fig. 3.—The squamous-cell carcinoma in situ (hematoxylin and eosin,  $\times 100$ ).

of 0.14 per cent. Seven cases of squamous-cell epithelioma of the cervix associated with prolapse of the uterus were found in the files of the Mayo Clinic in the years 1935 to 1947, inclusive. This gives an incidence of between 0.1 and 0.2 per cent of the cases of procidentia which agrees with the incidence reported

4. (Grading in this paper is on a basis of 1 to 4.) On the posterior lip of the cervix was a small, discrete, firm, white lesion, which bled on probing. Laboratory examinations revealed 13.9 Gm. of hemoglobin per 100 c.c. of blood. The leucocyte count was 5,500 cells per c.mm. Flocculation test for syphilis gave negative results. Pyuria, Grade 1, was noted on examination of a voided specimen of urine. Roentgenograms of the chest revealed nothing abnormal.



Fig. 1.—Atrophic uterus and small nodule in cervix.

On April 28, 1948, vaginal hysterectomy was performed, and the cystocele and rectocele were repaired. The pathologic specimen showed an atrophic uterus (Fig. 1). At the external os was a nodule measuring 1.5 cm. in diameter. The mucosa over this nodule appeared to be intact. The nodule was circumscribed and pinkish in appearance. On histologic examination, this nodule proved to be an adenocarcinoma of the cylindroma type. It was characterized by regular roundish cells which contained a small amount of cytoplasm. These cells were grouped in the typical cylindromatous pattern which most characteristically resembles the cut surface of Swiss cheese. In this pattern the cells enclosed multiple spaces, roundish to oval in shape, of a regular size. These spaces contained a secretion. Between the masses of neoplastic cells was fibrous tissue (Fig. 2). The epithelium overlying this neoplasm showed a noninfiltrative type of squamous-cell carcinoma, Grade 3, or carcinoma in situ (Fig. 3).

The patient made an uneventful recovery from the operation and was dismissed from the hospital on the sixteenth postoperative day.

### Comment

That carcinoma of the cervix associated with complete prolapse is a rare occurrence is evident from the few reports in the literature. In 1932, Guthrie and Bache<sup>6</sup> received 48 replies to questionnaires about this condition sent to

## II. HYALURONIDASE IN TREATMENT OF HUMAN STERILITY: ALLERGIC REACTION\*

LEO H. CRIEP, M.D., AND RALPH E. TAFEL, M.D., PITTSBURGH, PA.

**H**YALURONIDASE, an enzyme capable of hydrolyzing hyaluronic acid, has attained moderately widespread use in the treatment of sterility. Doubtful as its value in this connection seems to be, it is thought worth while to report a case of a local reaction encountered during its clinical application.

The enzyme hyaluronidase, a so-called "spreading factor," has been recommended in the treatment of human sterility by Kurzrok et al.<sup>1</sup> who have reported favorable results. The theoretical basis for the trial of hyaluronidase in this work rests upon several biological considerations,<sup>2, 3, 4</sup> most important of which is the fact that the enzyme is said to be capable of causing dispersal of the follicular cells of recently ovulated mammalian ova. The use of hyaluronidase implies acceptance of the belief that this disintegration of the corona is a prerequisite to fertilization of an ovum. It is not within the scope of this report to discuss the rationale or practicality of this employment of the enzyme. The method has not been successful in the hands of one of the authors of this paper (R. E. T.).

The hyaluronidase which was used in the treatment of sterility was derived from bovine testes. The bull testis hyaluronidase was provided by Schering and Co. It is protein in nature, and contains inorganic phosphorus and organic sulfur. One of us (R. E. T.) has collaborated in the experimental treatment of a series of 35 women. The technique in most instances was that suggested by Kurzrok, namely, the packing of 10 mg. of hyaluronidase into the cervix near to ovulation time, this application followed by intercourse within a few hours. Of the 35 women to whom a total of 90 treatments were administered, one complained of a troublesome local reaction following each of three cervical applications of the enzyme. None of the other patients experienced such discomfort.

### Case Report

Patient E. S., a white housewife, aged 40 years, married for 17 years, with a history of primary sterility, received three applications of hyaluronidase, one each on April 4, May 2, and May 24, 1947, by cervical packing. The reaction consisted of local irritation, oozing, and itching of the vagina and the external genitals. There were also general malaise, abdominal aching and cramping, some coughing, sneezing and lacrimation after each treatment. The reaction occurred in each instance sometime during the night a few hours after intercourse. The cervical application of hyaluronidase in each case was made about four o'clock in the afternoon. The patient herself believes that it is not the material itself that produces the irritation but rather intercourse with probable dispersal following the introduction of the material. It is noteworthy that reaction occurred after each administration of hyaluronidase including the first.

It was proposed to treat the patient with Pyribenzamine before the next treatment with hyaluronidase. The administration of Pyribenzamine, however, was followed by a

\*Second of three papers on hyaluronidase studies from the John C. Oliver Memorial Research Foundation and the Departments of Obstetrics-Gynecology, and of Urology, St. Margaret Memorial Hospital, Pittsburgh, Pa.

by Judd. Of these 7 cases, 5 were found to be cases of carcinoma in situ (intra-epithelial carcinoma). The other two were cases of early, infiltrating squamous-cell epitheliomas of the cervix, Stage I (classification of extent of growth on basis of I to IV). Emmert and Taussig<sup>4</sup> reported four cases, all of which were squamous-cell epitheliomas. In 77 of the 78 cases reported by Harvey and Ritchie,<sup>7</sup> epidermoid carcinoma was present, and in one case a sarcoma.

The reasons given for the rarity of this condition are numerous. Some protection may be afforded by the cornification of cervical epithelium which occurs when the cervix is outside the vagina. Indeed, cervixes in cases of procidentia have less areas of infection than the average cervix. There is also less vaginal secretion and relatively more free drainage. Usually uterine prolapse develops later in life than does cervical carcinoma. Women with prolapse often seek medical treatment earlier in the course than patients who have carcinoma. These last two factors did not hold true in the case reported herein. Definite reasons for the unusualness of this condition cannot be stated.

Vaginal hysterectomy seems to be the treatment most favored for cervical carcinoma in prolapsed uteri. At the same time coexisting cystocele and rectocele may be repaired. In view of the fact that most of these tumors are either early Stage I lesions or actually carcinomas in situ, this choice seems justified. However, Harvey and Ritchie favored radium therapy first, with subsequent operation if needed. Boukalik<sup>2</sup> reported one case in which treatment with radium alone resulted in cure of the prolapse and no evidence of recurrence of the carcinoma eleven and a half years after treatment. If, as a result of clinical examination and biopsy, the carcinoma is thought to have spread beyond the cervix, radium therapy would seem to be the more rational approach to the problem.

### Summary

Prolapse of the uterus complicated by carcinoma of the cervix is a rare condition. In the case of this type reported, vaginal hysterectomy and repair of vaginal relaxation were employed. The tumor proved to be an adenocarcinoma of cylindroma type. No other cases of cylindroma of the cervix were found in the literature. Vaginal hysterectomy is probably the treatment of choice in cases of prolapse of the uterus and carcinoma of the cervix if the cervical tumor is definitely a carcinoma in situ or of Stage I. Radium therapy should be used first if the carcinoma has extended beyond the cervix.

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# Department of Reviews and Abstracts

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## Selected Abstracts

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### Cancer, Malignancies

Stokes, E. Malcolm: The Association of Estrogenic Administration and Adenocarcinoma of the Endometrium, *West. J. Surg.*, page 494, Sept., 1948.

A carcinogen is a chemical or physical substance which applied under certain conditions induces a malignant tumor. Estrogen, chemically related to polycyclic hydrocarbons, is a carcinogen. Neoplastic cells arise from foci where rapid cell division is occurring in response to a repair or regeneration stimulus. When some external factor is introduced which interferes with the maturation of the normal cell enzyme pattern, the cells revert to the embryonic type. There is evidence to suggest that the estrogens accelerate such a reversion, possibly through their effects upon cell protoplasmic enzyme maturation.

There was a Negro woman, aged 65 years, 19 years postmenopausal, who received 470 doses of 0.1 mg. of stilbestrol over a period of 21 months. The uterus enlarged progressively and at operation an endometrial polyp with adenocarcinoma was found. It is the long, continuous administration of small estrogen doses that is more apt to cause carcinoma than the larger doses administered over shorter periods.

WILLIAM BICKERS.

Cabrera, G., and Guzman, F.: Sarcoma of the Fallopian Tube. Clinical Case Report, *Bol. Soc. chilena de obst. y ginec.* 13: 64-67, May, 1948.

The authors describe a rare case of primary sarcoma of the Fallopian tube in a 59-year-old patient with history of 8 deliveries and two spontaneous abortions. Her menopause occurred at age of 56 years. Pain and six days of vaginal bleeding were the first symptoms. She gained 13 kilograms in eight months. The tumor on the right tube measured 8.0 cm. in diameter and the microscopic diagnosis was sarcoma of the tube. Because of peritoneal implantations the patient received radiotherapy subsequent to surgery.

CLAIR E. FOLSOME.

Vergara, C. Casarin: Uterine Fibroids and Fundal Carcinoma, *Ginec. y obst. de Mexico* 3: 115-128, April, 1948.

Vergara reviews 4,012 operative cases seen in Pavillion 25 of the General Hospital in Mexico City between October, 1938, and August, 1947. Among these were 410 cases of uterine fibroids treated surgically. Ten of these cases, 2.5 per cent, presented coexisting adenocarcinomas of the fundus uteri.

The author concludes that any woman who bleeds in menopause should submit to hystero-graphy and endometrial biopsy although preferably a diagnostic dilatation and curettage. His treatment recommendation includes total hysterectomy.

The article includes three tables and fourteen illustrations. The photographs of thirteen hystero-graphs are striking in their bizarre shadows and illustrate well the intra-uterine patterns of coexistent fibroids and corporal carcinoma.

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marked skin eruption, and further applications of hyaluronidase were not attempted. The patient also states that she has been troubled for the last ten years with pruritus ani and has had various treatments for this condition without favorable results. However, this was not made worse during the course of the vaginal reactions to hyaluronidase.

The patient gives no history of any allergic manifestations, such as asthma, hay fever, hives, or eczema. There is no family history of allergy.

Intradermal tests with various dilutions of hyaluronidase extract gave uniformly negative results. Passive transfer was negative. A patch test performed on the skin close to the external genitals was negative; a scratch patch test with this material in the same area was slightly positive. The application of a small amount of hyaluronidase to the vaginal mucosa caused considerable irritation and exudation within a short time.

### Comment

A case of local contact dermatitis due to bull testis hyaluronidase is herewith reported. Apparently hyaluronidase is not a primary sensitizer. This case must be considered one of allergic type of eczematous contact dermatitis. The possibility of an atopic factor responsible for the respiratory symptoms must also be considered, even though the intradermal tests were negative.

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## Endometriosis

Gori, R. M.: Tubal Endometriosis, Endosalpingosis, *Obst. y ginec. latino-am.* 7: 242-264, June, 1948.

Gori restudied the pathology of Fallopian tubes taken from 862 patients over a period of twenty-five years in the Gynecology Clinic of Medical School of Buenos Aires. Among these cases the tubes showed no involvement in 146 instances; 24 cases of acute salpingitis; 16 subacute, and 291 cases of chronic salpingitis; 67 cases showing a tubercular process; 192 cases in which the tubes showed sequelae from chronic inflammatory change; 118 instances of tubal pregnancy; 4 cases of primary tubal carcinoma; 2 cases of hemorrhagic infarction, and one case each of actinomycosis and lymphosarcoma of the tubes. Among the 862 cases were found 77 patients showing endometriosis or endosalpingosis, an incidence of 8.9 per cent of the tubes examined.

The distribution of the endometriotic processes in the tubes were listed in the following groups: involvement of the interstitial portion and isthmus of the tube, 22 cases; involvement of the ampullar and distal end of the tube, 15 cases; diffuse process in the tube, 3 cases; peritoneal portion of the tube, 6 cases; endosalpingosis of the interstitial and isthmus of the tube, 16 cases; endosalpingosis of the ampullar and distal region of the tube, 8 cases; and endometriotic processes in tubal pregnancies, in 10 cases. Endometriosis was found in 5.9 per cent and endosalpingosis in 3.0 per cent of the cases; the former was found most often in the fourth decade and the latter diagnosis in the fifth decade. Dysmenorrhea was present in 73.6 per cent of the cases having endosalpingosis and in 45.9 per cent of the patients with endometriosis. The closer the endometriotic process was found to the uterus the greater was the incidence of dysmenorrhea as a symptom. Sterility was present in 52.1 per cent of the cases having endometriosis in the internal portion of the tubes as compared to 62 per cent sterility in patients having endosalpingitis. Uterine fibroids were found in 50 per cent of the series. Other localizations of the process besides the tube were found in 36 per cent of the cases. Among 113 tubal pregnancies, endometriotic lesions were found in 9.7 per cent of the series and in this group of tubal pregnancies there were 37.6 per cent of the group having associated fibroids. The author regards the Philipp and Huber modified theory of Sampson as the most logical to explain the pathogenesis of these processes. Seven tables and an unusually comprehensive bibliography accompany the article. CLAIR E. FOLSONE.

Brocq, Pierre: The Status of Endometriosis in Gynecology, *Rev. brasil. de cir.* 17: 289-296, June, 1948.

Since certain well-known French authorities still fail to recognize the entity of endometriosis, the author, a professor at the Paris Medical School, deems the subject worthy of factual review. First, he cites the pathological findings in the genital tissues, where endometriosis is much more frequently found, and then adds his observations anent the paragenital and extragenital findings in an excellent guest editorial. In the extragenital group he describes the lesions in the following order of frequency—the rectum, sigmoid, appendix, and the small intestines in the intestinal group; elsewhere, by order of frequency, the lesions are seen on the round ligament, the inguinal canal, laparotomy scars, perineal areas, and on the umbilicus. He cites three unusual cases of endometriosis located respectively on the thigh, the elbow, and the anterior surface of the forearm. He cites several cases, from the literature, that were most troublesome to explain from the pathogenic viewpoint; e.g., Gander's case of endometriosis of the scrotum in a male operated upon for hernia. The latter author mentions a similar second case in his article.

The author then considers endometriosis from the clinical viewpoint of the gynecologist, the surgeon, and the histologist. The surgeon generally regards these lesions as uncommon. The gynecologist regards it as essentially a pathological state seen frequently with other gynecologic conditions but primarily as a lesion producing the symptom of secondary dysmenorrhea. The pathologist decrees the poorer term endometrioma while the term adenomyo-

## Endocrinology

**Rauramo, Lauri:** The Level of Tocopherol (Vitamin E) in Blood Serum and Milk. The Values of Serum Tocopherol During Pregnancy and Lactation, *Acta obst. et gynec. Scandinav.* 27: Supplement 2, 1947.

The author completes an important contribution on tocopherol (Vitamin E) in its relation to pregnancy and lactation, in the dual departments of Biochemistry and Obstetrics and Gynecology at Helsinki University. His well-documented and extensive bibliographic report first reviews the influence of Vitamin E on tissue growth and hormone influences in laboratory animals. He then surveys numerous methods to evaluate tocopherol in blood serum and milk. To attain a greater degree of accuracy with microchemical methods he originates a new modification of the Emmerie-Engel dipyrindyl-fenichloride test and an original revision of Kofler's chromatographic adsorption procedure. In the latter he describes a more prolonged extraction method as well as a mechanical separation of the fluorescent portion of the chromatogram.

In his series of 53 nonpregnant women he noted 512 gamma per cent tocopherol value. Among the small group of normal mates the tocopherol value was found to be 416 gamma per cent. Tocopherol values were obtained throughout various phases of the menstrual cycle in the nonpregnant women. No significant changes were found related to any phase of the cycle.

Serum tocopherol values increased in the course of pregnancy gradually on a slowly climbing curve from the nonpregnant value of 513 gamma per cent up to an average of 1,131 gamma per cent immediately before delivery in a series of 32 pregnant women. There was only a slight fall during the first week after delivery, with an average value of 992 gamma per cent at the seventh postpartum day in the blood serum of sixteen women. During the first two months of nursing the serum tocopherol values returned gradually to nonpregnant figures but continued nursing reduces still more the serum tocopherol levels to an average of 300 gamma per cent. Large babies or sex of babies showed no reflection in the tocopherol serum level of the nursing mother.

The author, comparing his findings to serum level of tocopherol in nonpregnant cases in Holland and America, found lower figures in Holland and America than in Sweden. On the other hand he did find that the serum tocopherol level of pregnant women was the same value in Sweden and Holland.

One unique finding was that the tocopherol value in mother's milk was very high on the first day of nursing, varying from 1,000 to 3,480 gamma per cent in the first four days of nursing, but within 25 days from delivery the tocopherol content in maternal milk was generally under 300 gamma per cent.

The serum tocopherol average values in cows was 446 gamma per cent; for bulls 337 gamma per cent; for horses 156 gamma per cent and for pigs 85 gamma per cent. Rauramo was unable to find, with his methods, any measurable quantities of tocopherol in cow or goat milk being sold in Sweden.

Sixteen excellently prepared tables and a well-organized method of presenting his evidence in his 77-page study assist the reader in following the observations with ease.

CLAIRE E. FOLSOME.

**Nunez, A. Clavero:** The Use of Estrogens in the Differential Diagnosis of Metrorrhagias, *Revista Portuguesa de Obstetricia, Ginecologia e Cirurgia* 1: 189-190, June, 1948.

The author states that the bleeding from metropathia hemorrhagica can be distinguished easily from bleeding from incomplete abortion by injecting, in a single dose, 150,000 I. U. of dihydrofolliculin benzoate or any other natural estrogen of similar activity. If it is a question of metropathia hemorrhagica the bleeding lessens several hours later and ceases entirely the day following. The same method applies to menopausal bleeding which ceases if there is no organic pathology.

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came pregnant; however, only 93 of the group of 250 had a conceivable chance of pregnancy, making the percentage incidence 31.0 per cent. Among the 33 women having pregnancies, there was a total of 51 pregnancies, of which 33 went to term, three to premature delivery and fifteen resulted in miscarriage. In total, the mothers in this group gave birth to 36 living infants and one stillborn child. Spontaneous delivery occurred in 29 instances, forceps in five, and section was done on only one mother.

In five of the married women having conservative myomectomy, there was a history of three to fifteen years of preceding sterility. All these patients became pregnant within a year after surgery.

The author concludes that the uterus should be, as far as possible, left intact during the reproductive age period. He feels that the number of surgeons doing conservative operations for fibroids is increasing, although they are still far outnumbered by those who practice the too common total extirpation and, therefore, needless sacrifice of the uterus. Fifty-four tables and two figures are included in this excellent article which could well be read in detail by more American gynecologists and surgeons.

CLAIR E. FOLSOME.

**Palmer, Raoul:** Instrumentation and Technic of Gynecological Celioscopy, *Gynéc. et obst.* 46: 420-431, April, 1947.

Palmer reports his experiences after completing 250 gynecological celioscopies, with no untoward serious complications, and obtaining definite clinical information in 240 cases (96 per cent) in the series. Upon this justification he evaluates the techniques and methods in current use in gynecology. He describes three principal methods: (1) Irving Stein's method of outlining pelvic organs by pneumoperitoneum; (2) Kjellberg's method of introducing 40 to 80 c.c. of radiopaque solution via the transuterotubal route (hysterosalpingo-pelvigraphy) and (3) Decker's culdoscopic method. After using Decker's transvaginal approach, with patient in the knee-chest position, some ten times, Palmer considers it much inferior to the transabdominal celioscopic method for three reasons: (1) the vaginal route is least satisfactory from the point of asepsis; (2) while ovaries and tubes can be examined, the number of additional abdominal fields is limited because of difficult instrumentation through the vagina with patient in the knee-chest position, and (3) it is impossible to section adhesions from vaginal route but easy from the transabdominal route. The author does not summarize his clinical findings save as occasional cases to illustrate points of technique.

CLAIR E. FOLSOME.

**Thomas, Walter L., Carter, Bayard, and Parker, Roy T.:** Radical Panhysterectomy (Wertheim) and Radical Pelvic Lymphadenectomy, *South. M. J.* 41: 895, Oct., 1948.

Experience with radical hysterectomy and radical pelvic lymphadenectomy for the treatment of cancer of the cervix has been reviewed. Three groups of patients are compared: (1) patients with no previous irradiation; (2) patients who received x-ray therapy only or radium therapy only; (3) patients who, prior to operation, received complete radium and x-ray therapy. In the first group (44 per cent) there were eight (24 per cent) in whom pelvic lymph node metastases were found. In the second group (37 per cent) there were six (21.4 per cent) with positive nodes, and in the third group (15 per cent) there were two (18.2 per cent) with positive nodes. Microscopic findings in the radiated nodes showed definite evidence of radiation effects and it is probable that the cancer cells were destroyed in many of these lymph nodes before their surgical removal.

Seventy-five patients are reported with no death due to operation. Seven of these patients had adenocarcinoma of the cervix; and in this group it is felt that operation was definitely to be preferred to irradiation therapy. The same may be said for squamous-cell carcinoma of the cervical stump and squamous-cell carcinoma of the cervix complicated by early pregnancy. The majority of patients with carcinoma of the cervix will continue to be treated with the accepted techniques of irradiation therapy, but there is a small group in whom the surgical approach is preferred.

WILLIAM BICKERS.

sis can be used only when we are aware of specific pathological findings. Endometritis is an incorrect term. When considered in light of the metaplastic theory of pathogenesis the term *gynoblasts* would indicate those undifferentiated uterine cells capable of undergoing metaplastic change into endometrial elements. While the writer reviews in detail the theories and facts of the implantation and metaplasia hypotheses, and further cites a case he reported earlier with Varangot and Aschheim, wherein they found glandular elements in the veins of the myometrium during surgical care of a fibroid, the author believes that one cannot dismiss entirely the metaplasia theory. He cites Robert Meyer's suggestion that while endometrial fragments are capable, under selective influence, of destroying the musculo-elastic walls of vessels, they never pass the endothelial barriers.

In conclusion Brocq states that endometriosis, unrecognized by our forefathers, has a vastly distinctive position in our nosology. It should not be included either in the inflammatory states or the new growth categories. It is primarily a dysfunction related to increased estrogenic activity. As such it can be treated in two ways: by castration in the serious cases, or else by hormonal therapy in those exhibiting lesser symptomatology.

CLAIR E. FOLSOME.

Burnside, Alfred F.: *An Evaluation of the Treatment of Endometriosis*, South. Surgeon, page 645, Sept., 1948.

Endometriosis, its etiology, and treatment continue to be the object of speculation and theories. The author accepts the conclusions of Sampson that desquamated endometrial cells at the time of menstruation can regurgitate through the tubes and implant on the peritoneum. In support of the transplantation theory attention is called to certain cases of endometriosis in the abdominal wall following cesarean section.

Prophylactic measures which may be taken to prevent or stay the progress of endometriosis are correction of retroversion, dilatation of a stenosis, myomectomy, and discarding instruments during operation which have come in contact with the endometrium. Advanced pelvic endometriosis may be treated by x-ray which is often preferable to surgery. Limited experience with testosterone prompts the author to recommend it. Personal experiences in the treatment of this disease are cited which add nothing to the knowledge of the subject.

WILLIAM BICKERS.

## Gynecologic Operations

Ahlthrop, Gideon: *On Conservative Myomectomy. A Clinical and Statistical Investigation of the Indications and Technique Used, and the Results Obtained in Conservative Operations for Fibromyomas of the Uterus*, Acta obst. et gynec. Scandinav. 26: Supplement 6, 1946.

Ahlthrop surveys 282 cases of abdominal myomectomy and 46 cases of vaginal myomectomy done at Upsala University Hospital (1923 to 1931) and the Stockholm General Maternity Hospital (1931 to 1941). His 238-page report represents a classic on this important subject. He found conservative myomectomy used in less than 10 per cent of the total number of abdominal operations for fibroids. In a comparison of results of the conservative myomectomy to 572 cases of radical abdominal operations for fibroids, in the same period, the results of the former were more favorable. There was no mortality in the group operated upon conservatively and a 2.0 per cent mortality in the hysterectomized group.

Of 161 women undergoing enucleation of fibroids, 121, or 75.2 per cent, were free of recurrence. The risk of recurrence was found greater in cases where more than four fibroids were shelled out but even these percentages decrease as the increasing age of the patient is considered. Eight of the 242 cases of enucleation were reoperated upon (3.3 per cent). Seventy-five per cent of the patients treated conservatively had relief from menstrual distress. Thirty-three of 250 cases operated upon by conservative abdominal method afterward be-

endometrium, or definite absence of secretory activity to justify the diagnosis of anovulatory menstruation. The remainder of this subgroup (c) all exhibited scant secretory endometrial evidence. The sixteen cases of group (c) are individually documented and nine figures illustrate the article.

CLAIR E. FOLSOME.

**Bushnell, Lowell F.:** The Production of Ovulation in the Anovulatory Patient, West. J. Surg., page 556, Oct., 1948.

Failure to ovulate is assumed after four consecutive cycles of uterine bleeding from a proliferative endometrium and a concurrent basal body temperature curve showing no evidence of a biphasic curve. It is assumed that the anovulatory cycle is the result of either anterior lobe failure or antihormone inhibition. The patient is given 20 units of mare serum, gonadotropin, every 2 days during first half of the cycle and 40 units on the last 14 days of the last half. If a biphasic curve is induced, she is continued on this routine during subsequent months until pregnancy occurs. If biphasic curve does not result the dose may be increased to 50 units utilizing the same dose schedule of treatment. This treatment program may be used in the treatment of secondary amenorrhea, 40 per cent of these patients developing regular cycles after treatment. Administration of chorionic gonadotropin in the last half of the cycle favors luteinization of the endometrium. Approximately 50 per cent of anovulatory patients were induced to ovulate as indicated by thermal shift and endometrial response.

WILLIAM BICKERS.

**Benson, Ralph C.:** The Effect of Pitressin Tannate in Oil Upon Uterine Bleeding, West. J. Surg., page 440, Aug., 1948.

The physiology of menstruation and the current laboratory and clinical research related to it are presented in one of the best reviews of the subject to appear in recent clinical literature. It is evident from the endometrial transplant experiments of Markee and the anatomical studies upon the spiral end-arteries of the endometrium that menstruation is primarily a vascular phenomenon and more specifically arteriole in nature. The rate of blood flow through endometrial spiral arteries is influenced by myometrial contractions, the tortuosity of the spiral vessels, contraction of the radial arteries, and by the total blood volume passing through the uterine arteries. The volume of blood passing to the uterus can be reduced by means of Pitressin, the vasopressor hormone. Moreover, the nongravid uterus is highly irritable to Pitressin, but relatively nonreactive to Pitocin.

Pitressin tannate in oil was used for treatment of metrorrhagia and polymenorrhea in 100 patients, the dose being 1 c.c. of Pitressin in oil for 3 days. Through its action on the spiral arteries and the myometrium, uterine bleeding irrespective of etiology was successfully controlled in a large number of cases. The hormone is not curative, but most useful in the management of persistent and otherwise uncontrollable bleeding from the nongravid uterus.

WILLIAM BICKERS.

### Miscellaneous

**Van Ravesteyn, L. W.:** The Presence of Ascorbic Acid in the Follicular Cells of the Graafian Follicle in the Latter Phase of Development, the Preovulatory Phase, Acta Neerlandica Morphologiae Normalis et Pathologica 5: 285-301, 1945.

Van Ravesteyn, working in the Embryology and Histology Laboratory of Utrecht University, selected a special strain of white mice known for their high degree of fertility—47 generations in 9 years and known as the "047 Leeuwenhoekhuis of Amsterdam strain." The animals were sacrificed by decapitation, the ovaries and vagina removed, prepared with special fixatives of 10 per cent silver nitrate in the presence of strong acid (to precipitate in the cells, by reducing the silver salt with sodium bisulfite and light, the ascorbic acid) and then the

### Labor, Management, Complications

Abbas, T. M.: The importance of External Hysterography in the Study of Uterine Activity, *Edinburgh M. J.*, page 423, July, 1948.

The author presents several tracings of uterine activity made with a modified Dodek's tachodynamometer. One tracing of antenatal uterine activity confirms the findings of Murphy by demonstrating the large alpha waves and the small beta waves present prior to the onset of labor. Stimulation of the postpartum uterus with pituitary extract and physiologically at the time of nursing are also demonstrated. The irregularity of the contractions in uterine inertia is shown. Morphine reduced the amplitude and rate of uterine contractions in eight out of ten cases. Pethidine, on the other hand, increased the rate and progressively magnified the amplitude of the individual contractions in seven cases. In three cases, however, the contractions were not altered.

L. M. HELLMAN.

Beruti, J. A., Tenconi, J. L., and Tenconi, E.: A New Contribution to the Study of Transverse and Oblique Presentations, *Archivos de la Clinica Obstetrica y Ginecologica "Eliseo Canton"* 2: 349-365, Sept., 1943.

The authors classify the transverse and oblique fetal presentations into eight groups: dorsoanterior, posterior, superior, inferior, anterosuperior, posterosuperior, anteroinferior, and posteroinferior. To provide experimental roentgenographic evidence, they took numerous x-rays of a stillborn, placing his back convexly, into varied positions. They then describe seven new cases of transverse presentation and three cases with oblique presentation, with radiological data, from private cases seen in the Eliseo Canton Clinic in Buenos Aires.

The writers consider their studies to be important from a practical clinical management viewpoint. They had fewer diagnostic errors by distinguishing between the dorso-superior variety and the breech presentation. They indicate that there is a greater tendency for spontaneous correction, with facileness, by external version in some varieties but not in others. In the dorsosuperior presentation there was a tendency to premature rupture of the membranes. Three tracings illustrate the article.

CLAIR E. FOLSOME.

### Menstruation, Dysmenorrhea

Vignes, Henry: Amenorrhea Among Prisoners, *An. brasil. de gynec.* 24: 325-330, November, 1947.

The author, as one of a group of specialists, visited a concentration work camp at Drancy, after the liberation of Paris in September, 1944, sheltering about 9,000 prisoners of whom about 2,000 were women. Among the 676 cases with gynecologic symptoms were 154 instances of menstrual disorder among whom were 22 cases of menometrorrhagia, 128 cases of amenorrhea and four "mixed" cases. The author stresses the significance of emotional change upon the induction of amenorrhea in captive women.

CLAIR E. FOLSOME.

Uriegas, G., and Guerrero, C. D.: Anovulatory Menstruation in the Etiology of Sterility, *Ginec. y obst. de Mexico* 2: 209-238, June, 1947.

The authors review 105 consecutive cases of primary sterility in women. Among this group they found that 5.71 per cent exhibited anovulatory menstruation. Their criterion for study was based largely upon premenstrual endometrial biopsies. They grouped their series into three categories: group a, showing normal endometria, 43 cases; group b, showing histologic patterns suggesting decreased estrogenic activity but with some secretory activity, 46 cases; and group c, 16 cases, or 15.2 per cent of the series, exhibiting unusually atypical endometria. Among this latter group, six cases were found to have atrophic-like

employed to begin the transfusion, using matched blood to complete transfusion. If the father belongs to group O or A, and as the mother's blood (and therefore the infant's blood) will not contain anti-A agglutinins, a group A, Rh-negative donor can be used for the transfusion without determining the infant's blood group. But the donor cannot be chosen in advance if the mother belongs to group O and the father to group A, as, if the infant was of group O his serum would contain both alpha and beta antibodies and only a group O donor would be suitable; but if the infant belonged to group A, a group O donor could not be used because of alpha agglutinins in such a donor's plasma and a group A donor should be used. Analysis of other combinations, as given in the table, shows that an AB donor can be used for transfusion if the mother is of group AB, whether the father's blood group is O, A, B, or AB.

An illustrative case is reported in which the father was of group A, the mother of group AB, the father Rh-positive (Rh, rh) and the mother Rh-negative. Repeated determinations of the anti-Rh agglutinins in the mother's blood showed a rapid rise in titer during pregnancy of antibodies of the agglutinin type. An Rh-negative donor of group AB was selected for transfusion, and labor was induced two weeks before term. A replacement transfusion was given at birth using 500 c.c. of the donor's blood from which half the plasma was withdrawn using saline solution to make up the volume (to reduce the conglutinin content of the blood). The child made a good recovery, and the donor's blood cells survived in the infant's circulation for two months, although the infant was found to belong to group B.

HARVEY B. MATTHEWS.

**Watson, Janet:** The Significance of the Paucity of Sickle Cells in Newborn Negro Infants, *Am. J. M. Sc.* 215: 419, April, 1948.

In this communication an hypothesis is advanced to explain why there are relatively few sickle cells to be found in the blood of newborn infants whose blood later exhibits typical sickling.

The blood of 226 consecutive Negro newborn infants was studied. The mothers of these infants were used as controls. Sicklemia was found in eighteen of the mothers and nineteen of the newborns. This corresponds to the usual figure given for sicklemia in this country which is 7.3 per cent. In the series studied, 8 per cent of the mothers and 8.4 per cent of the infants had the disease. That sicklemia is Mendelian dominant is borne out by the fact that nine of the nineteen infants had mothers who also had the trait. Study of the blood of the mothers revealed that 84 to 100 per cent of the red cells showed sickling, whereas there was sickling in only 0.5 per cent to 29.5 per cent of the red cells of the infants. An explanation of the paucity of sickling in fetal blood is that it has been shown that fetal hemoglobin differs from adult hemoglobin. It is thought that this difference between the two is due to a variation in the chemical structure of the globin. Fetal hemoglobin thus appears to lack the sickling properties of adult hemoglobin. To substantiate this theory, studies were continued on infants showing sickling through the first four to six months of life. Since the estimated life span of the erythrocyte is four months, it would be expected that beyond this period of life marked sickling would occur. This is exactly what happened. Intrauterine death from sickle cell anemia has never been observed because fetal hemoglobin is unable to sickle even at the low oxygen tension which exists in the fetus.

HERBERT J. SIMON.

**Patrick, P. R.:** Report of a Survey of Children Born in 1941 With Reference to Congenital Abnormalities Arising From Maternal Rubella, *M. J. Australia*, vol. I, 35th yr. no. 14, p. 421, 1948.

The types of cases and abnormalities resulting from rubella in the mother contracted during pregnancy are reviewed. The figures continue to prove that the risk is greatest during the early months of pregnancy. The most frequent abnormality found was deafness;

tissue is serially sectioned. It is stained by Henke's method to provide more contrasting microphotographs.

The author found that the follicular cells always contain ascorbic acid in the last phase of maturation following the onset of estrus. The amount of ascorbic acid in the follicular cells is decreased slightly a little before ovulation. After ovulation, the ascorbic acid is concentrated, in the beginning, in the inner cell beds before the follicular cells. Following this, the ascorbic acid becomes more prominent in the external cellular beds while the corpus luteum is forming. The theca cells of the follicle contain ascorbic acid during ovulation and the follicular fluid gives, at the onset of the preovulatory phase, a very clear ascorbic acid reaction.

The article is well illustrated with seven microphotographs and well documented by data and bibliography.

CLAIR E. FOLSOME.

Portes, L., Granjon, A., and Heuville, A.: Tuberculosis and Twinning, *Gynéc. et obst.* 46: 112-115, 1947.

The authors, questioning the older observation that tuberculosis was a factor in twinning, decided to study the problem. From Baudelocque Clinic they reviewed twin cases born of tubercular mothers over the period from 1914 to 1944. They found 36 cases. In the twenty-three-year period, 1921 to 1944, 3,011 tubercular women had been hospitalized after abortion or delivery. Thirty had a history of twin delivery or abortion and one of a triplet abortion, or an incidence of 1.02 per cent of the total pregnancies. In a comparable period in France the twinning incidence was 1.10 to 1.20 per cent. In the same hospital from 1914 to 1944 there were 76,682 nontubercular pregnant cases. Among these were 781 instances of twin delivery or abortion, an incidence of 1.27 per cent.

In 30 years, 36 twin deliveries or abortions among a total of 981 had taken place in tubercular cases, or 3.67 per cent of twin cases. The 3,011 cases of pregnancy with tuberculosis represented 4.83 per cent tuberculosis among the pregnancy series. The authors conclude that tuberculosis is not a factor in twinning.

The prognosis of associated tuberculosis and twin pregnancy was found poor. Maternal mortality was 17.0 per cent in the month following delivery as compared to 2.9 per cent in the nontubercular mothers giving birth to twins. The over-all tubercular maternal mortality was 4.8 per cent. The fetal mortality in tubercular mothers with twins, sixth month of pregnancy to the first thirty days after delivery, was 26.6 per cent, as compared to 20.9 per cent in nontubercular women having twins.

CLAIR E. FOLSOME.

### Newborn

Wiener, A. S., and Wexler, I. B.: Antenatal Selection of Donors for Exchange Transfusion in Erythroblastosis, *Anesthesiology* 9: 296, 1948.

In the treatment of erythroblastosis fetalis, replacement transfusion is employed. If this is to prevent permanent tissue damage, such a transfusion should be given immediately after birth, and it is desirable to select a suitable donor for the transfusion before the birth of the child. This can often be done by determining the blood group of the mother and father. Since the fetus and the newborn infant do not produce antibodies, the only antibodies in the blood of the infant at birth are derived from the mother; the mother's blood group, therefore, is an important consideration. A table is presented showing the blood group from which a donor can be selected when the blood group of the mother and father are determined. In some cases, however, the donor cannot be selected until the infant's blood group is determined from the cord blood. If a compatible donor is not available in cases of great urgency, group O blood to which Witebsky's A and B substance has been added to neutralize the alpha and beta antibodies may be

There was a rapid increase in the radioactive phosphorus turnover in the hypophyseal-diencephalic system in relation to coition, the increase appearing distinctly in appreciable values in two minutes after coitus. The increased activity is maintained in the tuber cinereum during the first postcoital hour. The pars glandularis of the hypophysis gave an increased activity postcoitally which was maintained for 24 hours with peak activity at the second half-hour period after coition. An increase was demonstrated postcoitally in ovaries but not appearing until thirty minutes after coitus. The high level in ovaries is maintained reaching a new maximal plane in nine to eleven hours after coitus; i.e., when ovulation occurs. Upon the basis of these observations the authors conclude that the hypophyseal-diencephalic system constitutes a functional unit to play a conclusive part in ovulation. CLAIR E. FOLSOME.

Kahanpaa, V.: A New Simplified Radium Applicator for Intensifying the Radiotherapy of the Parametria in Cancer of the Cervix, *Acta Radiol.* 27: 495-504, 1946.

Kahanpaa, of the Central Institute for Radiotherapy, Helsinki, develops a new vaginal applicator from stainless steel plate in the shape of a narrow "U." The radium bolts are placed at ends of both distal limbs of the "U" which are bent outwardly. These spring tension causes powerful lateral pressure. At the same time a tight Y bandage over the bow end of the applicator pushes the radium-containing bolts higher up into the parametrial regions. This permits a 1,000 mg. hr. greater dosage in vaginal radium treatment than was possible with other applicators because the rectal wall is displaced more effectively out of the way during treatment, thus increasing the ability to deliver a greater parametrial radium dosage via vaginal route. The author, after experience with 35 cases, states the applicator is now part of the regular equipment at their clinic along with the otherwise three-phase method of Stockholm. Ten illustrations are included. CLAIR E. FOLSOME.

### Sterility, Fertility, Contraceptives

Chastrusse, M. L.: Artificial Insemination in Woman, *J. de méd. de Bordeaux* 125: 1-15, Jan., 1948.

The author reviews the history of insemination in women and animals in a lengthy article. He includes many new references not familiar to American workers in this field. He divides his discussion into numerous headings including (1) the indications; (2) contra-indications; (3) the technique, under which he considers (a) the choice of the donor, (b) evaluation of the semen specimen, (c) the time for insemination, and (d) the technique for introduction of sperm; (4) the legal aspects; (5) the moral aspects and (6) the religious considerations.

The author offers no case studies, only a well-phrased review. His contribution is important because of his discussion of considerable literature not available in the States. In summary, the author condemns heterologous insemination heartily and states homologous insemination is indicated only in organic maldevelopments or previous genital injury in the married couple. The insemination technique should always be only vaginal in type.

CLAIR E. FOLSOME.

Murray, E. G.: Extragenital Pelvic Pathology in Sterility, *Ginec. y obst. de Mexico* 3: 167-180, 1948.

Murray, of Buenos Aires, selects from 652 sterility cases, seen at the Sterility Clinic of the Pedro A. Pardo Lying-In Hospital, 66 patients presenting extragenital pelvic pathology which he considers pertinent to the sterility etiology. The author believes that this group of 12.5 per cent of female sterility etiology, the peritoneal factor, is often neglected in case study and treatment. He divides these "blockings" into several categories: ovarian (ovulation precluded by intrinsic or extrinsic layering of resistant fibrous tissue or serosa); tubal

then followed congenital heart disease, mental deficiency, and finally cataracts. The authors conclude that despite the lack of experimental evidence, there is sufficient clinical evidence in this and other reports to show the grave risk of exposure of the pregnant woman to rubella. Certain preventive measures are outlined to prevent these abnormalities. The treatment and education of the handicapped are also outlined.

WILLIAM BERMAN.

### Pregnancy, Complications

O'Hanlon, R. H., and Stewart, F. S.: Maternal Jaundice in Association With Hemolytic Disease Due to Rh Sensitization, Irish J. M. Sc., 1948.

Two cases of coincidental maternal jaundice in Rh sensitization are presented. In one, the mother gave birth to an infant with relatively mild hemolytic disease. In the other, the infant was hydropic. The authors do not establish any causal relationship between the maternal jaundice and hemolytic disease.

L. M. HELLMAN.

Whitelaw, M. James: Thiouracil in the Treatment of Hyperthyroidism Complicating Pregnancy and Its Effect on the Human Fetal Thyroid, J. Clin. Endocrinol., November, 1947.

The literature to date of cases of hyperthyroidism, complicated by pregnancy and treated with thiouracil, is reviewed. A case is then reported of a patient exhibiting marked thyrotoxicosis (basal metabolism rate plus 65 per cent) who was hospitalized in her twenty-sixth week of pregnancy. Thiouracil treatment was instituted and continued until the forty-first week of her pregnancy when she delivered an encephalic male monster. The infant survived six hours and ten minutes. After death the thyroid gland was removed. The gland was found to be slightly smaller than the reported normal, there was no diminution of the iodine content, and the histologic appearance was normal.

Thus, it would appear, based on a single case, that the administration of thiouracil to a hyperthyroid pregnant female has no demonstrable injurious effect on the newborn.

HERBERT J. SIMON.

### Radiation

Borell, U., Westmann, A., and Orstrom, A.: Studies on the Functions of the Hypophyseal-Diencephalic System and of the Ovaries by Means of Radioactive Phosphorus, Gynaecologia 123: 186-200, March, 1947.

The authors, reporting from the Gynecology Clinic at Caroline Hospital, Stockholm, determined to find a way to demonstrate the possible role that the nervous centers in the hypothalamus might play in ovarian function beyond the known hypophyseal factors. They selected the rabbit as the best suited experimental animal because the maturation and rupture of the follicles occur only after intercourse or strong sexual stimulus. Radioactive phosphorus as free phosphorus,  $P^{32}$ , in 5 per cent glucose solution, was injected intravenously into anestrus and estrus females at predetermined intervals before and after coitus. Castrate animals were also examined three to five weeks after oophorectomy. Each animal received 0.1 mc. in 1.0 c.c. Thirty minutes after injection the animals were killed by decapitation to remove all possible blood from organs. The blood, cerebellum, tuber cinereum, pars glandularis of the hypophysis, and the ovaries were examined for total radioactivity and total phosphate.

For the tuber cinereum, adenohypophysis, and ovaries the authors found no difference in phosphate turnover between the anestrus and estrus female rabbits. In castrate animals they found an appreciable increase in the phosphate turnover in the adenohypophysis and no increase in the tuber cinereum.



fifth month of pregnancy. The larvae were studied and diagnosed as those of *Cochliomyia hominivorax*. Treatment consisted of intravenous injections of a mercury compound, Arsenox, and penicillin. Four pictures illustrate the lesion, larvae, and insects. CLAIR E. FOLSOME.

Férrer, D. Lopez: Some Considerations on Vaginal Trichomoniasis, Ginec. y obst. de Mexico 2: 451-455, Dec., 1947.

The author reviewed the pelvic findings of 500 consecutive obstetrical and gynecological cases seen at Maximo Avila Camacho Center, Mexico, to evaluate vaginal trichomoniasis. From the 500 cases seen, 437 of them, 87.4 per cent, presented leucorrhea of several types. Of this series 83 women, or 19.2 per cent, had demonstrable trichomonads in their leucorrheal secretions, and while 104 cases of the 437 women having leucorrhea (20.8 per cent) had pruritus, it was found as a symptom in thirty-six instances of the 83 cases (34.61 per cent) having trichomonorrhea.

The patients were treated with silver picate suppositories with or without acidulated douches for a time interval of eight days to six months. There were two cases refractive to this treatment and none showed intolerance to the local drugs used. The author's breakdown of his figures on the incidence of this infestation and on correlation of symptoms to type of leucorrhea in pregnant and nonpregnant patients is well done. He finds trichomoniasis of greater frequency in pregnant and sterility cases and the symptom of pruritus a more constant finding when this infestation is the chief etiologic factor in leucorrhea.

CLAIR E. FOLSOME.

Chavarria, H. M.: The Treatment of Trichomonas Vaginitis. The Action of Topical Estrogens, Bol. de la Soc. de obst. y ginec. de Buenos Aires 26: 536-544, Nov. 13, 1947.

The author feels there are cyclic aggressions of trichomonads accounting for increased epithelial destruction periodically. This increased activity of trichomonas seems to occur at periods of lowered estrogen levels. To offer resistance to destruction of the mucosal stratification, he used local estrogenic therapy only in fifty-five cases, all observed over a long period of time. He not only obtained relief in a large number of cases but was able to clear up some unusually resistant cases. He outlines his rationalization in clear terms and this is enlarged upon considerably by numerous discussants of his paper. He relies not entirely upon local estrogens, but deems them important as supplemental local treatment.

CLAIR E. FOLSOME.

Branscomb, Louise: Mycotic Vulvovaginitis, South. M. J. 41: 534, June, 1948.

Severe itching of the vulva and vagina will often result in mycotic infection. Microscopic examination of the vaginal secretion on wet smear often fails to reveal the mycelium or buds, or yeast fungi; while culture on Sabouraud's medium confirms the diagnosis. A simple culture method is described in which the vaginal secretion is allowed to stand in saline for forty-eight hours, during which time the growth of yeast fungus occurs and microscopic detection is facilitated.

Treatment of fifty-one private patients with propionate jelly is described. Vaginal insertion of the jelly twice daily for twenty days was prescribed. A majority were relieved of itching within seventy-two hours and thirty-three were cured at the end of three weeks. Where skin involvement of the vulva is present, propionate jelly is inadequate for cure. It must be supplemented by gentian violet.

WILLIAM BICKERS.

(obstructed fimbria); and peritoneal (malpositions of upper generative organs by adhesions and old adherent exudates). He believes also that there exist functional "blockings" when the distance between the ovary and the fimbria is increased due to the retraction of the mesentery of or ligament of the ovary and/or tube.

The author illustrates the value of salpingohysterography in the diagnosis of these "blocking" factors. Treatment is usually surgical. Twenty-three cases, 34.8 per cent, were so treated. From this group he has obtained four full-term pregnancies, a success of 17.39 per cent following surgery. Eleven figures illustrate the article. CLAIR E. FOLSOME.

### Tubal Insufflation

Nielsen, Povl Holm: *Injuries Caused by Hysterosalpingography*, *Acta obst. et gynec. Scandinav.* 26: 565-597, 1946.

Nielsen, from the University Clinic of the Aarhus Municipal Hospital, Denmark, reviews the experience of hysterosalpingography, with the use of iodized oils only, in his own clinic and from questionnaires sent to one hundred thirteen Danish hospitals excluding only those with ten beds or less. He estimates 12,000 studies were done by the hospital group receiving the questionnaire and 1,098 more were done on 982 patients at his clinic between June 1, 1940, and Sept. 1, 1944.

The one hundred thirteen Danish hospital groups were divided into three classifications: A, departments of obstetrics and gynecology, ten in number; B, forty departments of surgery; and C, sixty one-department hospitals. The three additional questionnaires overlapped radiological groups in larger hospitals with both types of service. In Group A, all used hysterosalpingography and five reported no complications; the five others reported ten, plus "a few" cases of flareup of salpingitis or parametritis; and one reported one case of perforation of uterus. In Group B, thirty-three of forty surgery departments used this method and twenty-eight of these had had no complications. The five others reported five re-exacerbations of salpingitis and two fatalities (peritonitis). Among Group C, only thirty-one of the sixty one-department hospitals used the method, while twenty-eight of these had no complications and the remainder reported a scant number of salpingitis recurrences. Only a few hospitals used Lipiodol, most using other iodized oil preparations including Iodipin, Iodumbrin, Perabrodil, Hippodin, or more lately Uroselectan B.

The author found twenty-two patients among his own clinic series of 982 cases (1,098 hysterosalpingograms) exhibiting mild symptoms (mild temperature rise of 0.5 to 1.0 degree) and seven cases with more marked or protracted symptoms. All seven cases had mild to moderate recurrence of salpingitis.

Nielsen concludes that he could find no evidence of iodine intoxication, one case of uterine perforation, five cases of contrast media introduced into uterine vessels, and that he could find no evidence to indicate that hysterosalpingography increased the disposition to extrauterine pregnancy. He further concludes that while the technique is simple, it is not an insignificant intervention, but that its use in clinical gynecology is immensely important. Statistically, the chance for flare-up of inflammatory change is 0.25 per cent, while the chance of death is 0.1 to 0.2 per 1,000. CLAIR E. FOLSOME.

### Vaginal Infections

Da Silva Pereira, J. M.: *Myiasis of the Vulva*, *An. brasil. de. gynec.* 24: 331-340, Nov., 1947.

The author presents a review of the rare disease, myiasis of the vulva, and adds a new case to the literature. His case was present in a 17-year-old Negro pregnant woman in her

# ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES\*

(Appears in January, April, July, October)

- American Gynecological Society.** (1876) *President*, Joseph Baer. *Secretary*, Norman F. Miller, 1313 East Ann St., Ann Arbor, Mich. Next meeting, May 11, 12, 13, 1950, The Greenbrier, White Sulphur Springs, Va.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons.** (1888) *President*, James R. Bloss, Huntington, W. Va. *Secretary*, Leroy A. Calkins, 418 11th Street, Huntington, W. Va. Annual meeting Hot Springs, Va., Sept. 7-9, 1949.
- Central Association of Obstetricians and Gynecologists.** (1929) *President*, Earl C. Sage, Omaha, Neb. *Secretary-Treasurer*, John I. Brewer, 104 South Michigan Ave., Chicago, Ill. Annual meeting Oklahoma City, Okla., Nov. 3, 4, and 5, 1949, Municipal Auditorium.
- South Atlantic Association of Obstetricians and Gynecologists.** (1938) *President*, C. J. Andrews, Norfolk, Va. *Secretary*, E. D. Colvin, 1259 Clifton Road, N.E., Atlanta, Ga. Next meeting, Feb. 9, 10, and 11, 1950, Hotel Roanoke, Roanoke, Va.
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, William F. Mengert, Dallas, Texas. *Secretary*, A. B. Hunt, Mayo Clinic, Rochester, Minn. Annual meeting June, 1950.
- New York Obstetrical Society.** (1863) *President*, Albert H. Aldridge. *Secretary*, Claude E. Heaton, 205 East 69th St., New York 21, N. Y. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia.** (1868) *President*, Carl Bachman. *Secretary*, George A. Hahn, 255 S. 17th St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society.** (1878) *President*, Herbert E. Schmitz. *Secretary*, Edward M. Dorr, 30 N. Michigan Ave., Chicago 2, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society.** (1890) *President*, Henry S. Acken, Jr. *Secretary*, J. Edward Hall, 429 Clinton Avenue, Brooklyn 5, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society.** (1929) *President*, Houston S. Everett. *Secretary-Treasurer*, W. Drummond Eaton, 11 E. Chase St., Baltimore 2, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.
- Cincinnati Obstetrical Society.** (1876) *President*, Edward Friedman. *Secretary*, Lester J. Bossert, 2404 Auburn Ave., Cincinnati 19, Ohio. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society.** *President*, Rudy F. Vogt. *Secretary-Treasurer*, Glenn W. Bryant, Louisville, Ky. Meetings fourth Monday of each month from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology.** *President*, Ronald Frazier. *Secretary-Treasurer*, Gifford D. Seitz, 919 Taylor St. Bldg., Portland 5, Ore. Meetings last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society.** (1934) *President*, R. A. D. Gillis. *Secretary*, Clarence H. Ingram, Jr., 902 Peoples East End Building, Pittsburgh 6, Pa. First Monday of October, November, December, January, February, March, April, and May.
- Obstetrical Society of Boston.** (1861) *President*, M. Fletcher Eades. *Secretary*, H. Bristol Nelson, 1180 Beacon Street, Brookline, Mass. Third Tuesday, October to April, Harvard Club.
- New England Obstetrical and Gynecological Society.** (1929) *President*, Arthur E. G. Edgelow, Springfield, Mass. *Recorder*, Carmi R. Alden, 270 Commonwealth Ave., Boston 16, Mass. Meetings held in May and December.
- Pacific Coast Obstetrical and Gynecological Society.** (1931) *President*, Philip H. Arnot. *Secretary-Treasurer*, R. Glenn Craig, 490 Post St., San Francisco, Calif.
- Washington Gynecological Society.** (1933) *President*, Henry L. Darner. *Secretary*, John Parks, 901 23 St., N.W., Washington, D. C. Fourth Saturday, October, November, January, March, May.
- New Orleans Obstetrical and Gynecological Society.** (1924) *President*, Conrad G. Collins. *Secretary*, E. W. Nelson, 1407 S. Carrollton Ave., New Orleans. La. Meetings held October, November, January, March, and May.

\*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the Society's name is the year of founding.

## Items

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### **The International and Fourth American Congress on Obstetrics and Gynecology**

The Scientific and Educational Exhibit Committee of the International and Fourth American Congress on Obstetrics and Gynecology under the Chairmanship of Dr. John Parks of Washington, D. C., and the Committee on Motion Pictures with Dr. Archibald D. Campbell of Montreal, Canada, as Chairman have completed preliminary plans for their respective sections of the meeting and are ready to issue application blanks for space and time. These blanks are designed to facilitate the work of the committees in selecting and presenting exhibits and films of the greatest value and to make it easy for the applicants to present a complete description of their proposed displays. They will be sent on request by the business office of the American Congress at 24 West Ohio Street, Chicago 10, Ill., and, when completed, go directly to the chairman of the committee involved.

The members of the Scientific and Educational Exhibit Committee working with Doctor Parks are: Dr. Miguel V. Falsia of Buenos Aires, Sir Eardley Holland of London, Dr. Mortimer N. Hyams of New York, Dr. Alice F. Maxwell of San Francisco, Dr. Lawrence M. Randall of Rochester, Dr. Jorge de Rezende of Rio de Janeiro, Dr. Erik Rydberg of Copenhagen, Dr. Donald G. Tollefson of Los Angeles, and Dr. Frank E. Whitacre of Memphis.

The members of the Committee on Motion Pictures working with Dr. Campbell are: Dr. David N. Barrows of New York, Dr. Willard R. Cooke of Galveston, Dr. Samuel A. Cosgrove of Jersey City, Dr. Carl Henry Davis of Wilmington, Dr. Ludwig A. Emge of San Francisco, Dr. Albert W. Holman of Portland, Dr. Edmundo G. Murray of Buenos Aires, and Dr. Robert A. Ross of Durham.

The scientific program is in charge of Dr. Howard C. Taylor, 842 Park Avenue, New York City 21, New York, U. S. A. Those desiring to contribute should address him at an early date for further information.

### **American Board of Obstetrics and Gynecology**

The American Board of Obstetrics and Gynecology in annual session in Chicago, Ill., May 8 to 14, 1949, announced the election of the following officers:

Walter T. Daínreuther, M.D., President, New York, N. Y.

Joseph L. Baer, M.D., Vice-President, Chicago, Ill.

Willard R. Cooke, M.D., Vice-President, Galveston, Texas.

Paul Titus, M.D., Secretary-Treasurer, 1015 Highland Building, Pittsburgh, Pa.

Robert L. Faulkner, M.D., Assistant Secretary, 2105 Adelbert Road, Cleveland, Ohio.

The other Directors of the Board are:

F. Bayard Carter, M.D., Duke University, Durham, N. C.

Daniel G. Morton, M.D., University of California Hospital, San Francisco, Calif.

Robert A. Kimbrough, Jr., M.D., 807 Spruce Street, Philadelphia, Pa.

Lawrence M. Randall, M.D., Mayo Clinic, Rochester, Minn.

The next annual examination meeting will be held at the Hotel Shelburne in Atlantic City, New Jersey, May 21 to 28, 1950, immediately following the International Congress on Obstetrics and Gynecology in New York.

- Omaha Obstetrical and Gynecological Society.** (1947) *President*, Harley E. Anderson. *Secretary*, Donald C. Vroman, 813 Medical Arts Bldg., Omaha 2, Neb. Meetings held third Wednesday in January, March, May, September, November.
- Oklahoma City Obstetrical and Gynecological Society.** (1940) *President*, John W. Records. *Secretary-Treasurer*, Henry G. Bennett, Jr., 800 Northeast 13 Street, Oklahoma City 4.
- Cleveland Obstetrical and Gynecological Society.** (1947) *President*, Robert E. Faulkner. *Secretary*, G. Keith Folger, 10515 Carnegie Ave. Meetings on fourth Tuesday of September, November, January, March, and May at University Club, 3813 Euclid Ave., Cleveland 15, Ohio.
- New Jersey Obstetrical and Gynecological Society.** (1947) *President*, Herschel Murphy. *Secretary*, Benjamin Daversa, Spring Lake, N. J. Meetings semiannually.
- Honolulu Obstetrical and Gynecological Society.** (1947) *President*, Frank C. Spencer. *Secretary-Treasurer*, H. McLeod Patterson, 202 King Kalakaua Bldg., Honolulu, Hawaii. Meetings third Monday of each month, Mabel Smyth Building.
- Oregon Society of Obstetricians and Gynecologists.** *President*, Gerald Kinzel. *Secretary-Treasurer*, Theodore M. Bischoff, 529 Mayer Bldg., Portland 5, Ore. Meetings held on third Friday of each month from October to May.
- National Federation of Obstetric-Gynecologic Societies.** (1945) *President*, Ralph E. Campbell. *Secretary*, Woodard D. Beacham, 429 Hutchinson Memorial Bldg., New Orleans 13, La.
- Dayton Obstetrical and Gynecological Society.** (1937) *President*, A. D. Cook. *Secretary*, L. O. Frederick, 413 Third National Bldg., Dayton 2, Ohio. Meetings, third Wednesday monthly from September through June at the Van Cleve Hotel.
- Dallas-Fort Worth Obstetric and Gynecologic Society.** (1948) *President*, Asa A. Newsom. *Secretary*, A. W. Diddle, 2211 Oak Lawn Ave., Dallas 4, Texas. Meetings in spring and fall.
- Queens Gynecological Society.** (1948) *President*, Edward C. Veprovsky. *Secretary*, George Schaefer, 112-25 Queens Blvd., Forest Hills, N. Y. Meetings held second Wednesday in February, April, October, and December, at the Queens County Medical Society Bldg.
- Mississippi Association of Obstetricians and Gynecologists.** (1947) *President*, Walter Simmons. *Secretary*, Richard H. Street, Jr., The Street Clinic, Vicksburg, Miss. Meetings held semiannually.
- Florida Obstetrical and Gynecological Society.** *President*, Charles J. Collins. *Secretary*, Dorothy D. Brame, Orlando, Fla. Next annual meeting, Belleair, April 10, 1949.
- South Carolina Obstetrical and Gynecological Society.** (1946) *President*, J. Decherd Guess. *Secretary*, Arthur L. Rivers, 231 Calhoun St., Charleston, S. C. Meetings held in spring and fall.
- Buffalo Obstetrical and Gynecological Society.** (1946) *President*, W. Herbert Burwig. *Secretary*, Clyde L. Randall, 925 Delaware Avenue, Buffalo, N. Y. Meetings held on the first Tuesday of October through May at the Saturn Club.
- El Paso Gynecological Society.** (1948) *President*, Gerald H. Jordan. *Secretary-Treasurer*, Gray E. Carpenter, 303 N. Oregon St., El Paso, Texas.
- Kentucky Obstetrical and Gynecological Society.** (1947) *President*, W. O. Johnson. *Secretary*, Edwin P. Solomon, 910 Heyburn Bldg., Louisville, Ky.
- Indianapolis Obstetrical and Gynecological Society.** (1947) *President*, David L. Smith. *Secretary*, Sprague H. Gardiner, 314 Hume Mansur Bldg., Indianapolis 4, Ind. Meetings held in January, April, and October.
- Houston Obstetrical and Gynecological Society.** (1939) *President*, John A. Wall. *Secretary-Treasurer*, Herman L. Gardner, Hermann Professional Bldg., Houston 5, Texas. Meetings held second Tuesday of each month except July, August, and September.
- Iowa Obstetric and Gynecologic Society.** *President*, J. H. Randall. *Secretary*, William C. Keettel, Iowa City, Iowa.

- St. Louis Gynecological Society.** (1924) *President*, A. N. Arneson. *Secretary*, Paul F. Fletcher, 634 North Grand Ave., St. Louis 3, Mo. Meetings second Thursday, October, December, February, and April.
- San Francisco Gynecological Society.** (1929) *President*, Albert M. Vollmer. *Secretary*, Donald W. de Carle, 2000 Van Ness Ave., San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists.** (1930) *President*, Julius McIver, Dallas. *Secretary*, George F. Adam, 4115 Fannin St., Houston 4, Tex. Annual meeting, Dallas, Texas, September, 1949.
- Michigan Society of Obstetricians and Gynecologists.** (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President*, O. W. Picard. *Secretary*, Carl F. Shelton, 910 David Broderick Tower, Detroit 26, Mich. Meetings first Tuesday of each month from October to May (inclusive).
- Central New York Association of Gynecologists and Obstetricians.** (1938) *President*, Louis G. Fournier. *Secretary*, Merton C. Hatch, Medical Arts Bldg., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.
- Alabama Association of Obstetricians and Gynecologists.** *President*, Gilbert F. Douglas. *Secretary*, Hunter Brown, 1922 South Tenth Ave., Birmingham, Ala.
- San Antonio Obstetric Society.** *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.
- Seattle Gynecological Society.** (1941) *President*, Donald J. Thorp. *Secretary-Treasurer*, Charles D. Kimball, 734 Broadway, Seattle 22, Wash. Meetings held on third Wednesday of each month, Washington Athletic Club.
- Denver Gynecological and Obstetrical Society.** (1942) *President*, Lyman W. Mason. *Secretary-Treasurer*, Jack M. Simmons, Jr., 638 Republic Bldg., Denver 2, Colo. Meetings held first Monday of every month from October to May (inclusive).
- Wisconsin Society of Obstetrics and Gynecology.** (1940) *President*, Henry A. Sincock. *Secretary-Treasurer*, Edith McCann, 425 East Wisconsin Ave., Milwaukee 2. Meetings held in May and October.
- San Diego Gynecological Society.** (1937) *President*, P. L. Martin. *Secretary*, Albert P. Kimball, 233 "A" St., San Diego, Calif. Meetings held on the last Friday of each month.
- North Dakota Society of Obstetrics and Gynecology.** (1938) *President*, H. A. Wheeler, Grand Forks. *Secretary*, C. B. Darner, Fargo, N. D.
- Virginia Obstetrical and Gynecological Society.** (1936) *President*, Walter McMann. *Secretary-Treasurer*, L. L. Shamburger, State Health Department, Richmond, Va. Next meeting not announced.
- Columbus Obstetric and Gynecologic Society.** (1944) *President*, Wayne Brehm. *Secretary*, Zeph J. R. Hollenbeck, 9 Buttles Ave., Columbus, Ohio. Meetings held fourth Wednesday of each month.
- Naussau Obstetrical Society.** (1944) *President*, Robert S. Millen. *Secretary-Treasurer*, Peter La Mariana, Williston Park, L. I., N. Y. Meetings, bimonthly from October to May.
- Bronx Gynecological and Obstetrical Society.** (1924) *President*, Charles W. Frank. *Secretary*, Benjamin Karen, 1100 Grand Concourse, New York 56, N. Y. Meetings, fourth Monday monthly from October to May.
- Washington State Obstetrical Society.** (1936) *President*, John H. Fiorino, Everett. *Secretary*, C. Wendell Knudson, Medical and Dental Bldg., Seattle, Wash. Meetings, first Saturday of April and October.
- Kansas City Obstetrical and Gynecological Society.** (1922) *President*, Joseph G. Webster. *Secretary*, William C. Mixson, 320 W. 47th St., Kansas City, Mo. Meetings, last Thursday, September, November, January, and March; first Thursday, May, University Club.
- Los Angeles Obstetrical and Gynecological Society.** (1914) *President*, L. G. Baldwin. *Secretary-Treasurer*, Gordon Rosenblum, 6333 Wilshire Blvd., Los Angeles 36, Calif.
- North Carolina Obstetrical and Gynecological Society.** (1932) *President*, Wallace B. Bradford. *Secretary*, Richard B. Dunn. Meetings semiannually.
- The Society of Obstetricians and Gynecologists of Canada.** (1944) *President*, J. Ross Vant. *Secretary*, J. O. Baker, Edmonton, Alberta. Annual meeting, June 18 to 22, 1949, at Jasper Park Lodge, Jasper National Parks.
- Akron Obstetrical and Gynecological Society.** (1946) *President*, George A. Palmer. *Secretary-Treasurer*, Alven M. Weil, 1030 First National Tower, Akron 8, Ohio. Meetings held third Friday of January, April, July, and October, City Club of Akron, Ohio, Bldg.
- Minnesota Society of Obstetrics and Gynecology.** *President*, Russell J. Moe. *Secretary*, John Haugen, 100 E. Franklin, Minneapolis, Minn. Meetings held spring and fall.
- Miami Obstetrical and Gynecological Society.** (1946) *President*, Homer L. Pearson. *Secretary*, John D. Milton, 1104 Huntington Bldg., Miami, Fla. Meetings, second Thursday in January, March, May, and November.

(obstetrics) and the pathology (gynecology) of these organs into two specialties? Pregnant women have fibroids; those with malignant tumors become pregnant, and to pursue farther, if necessary, the absurdity of artificial division, who will treat the surgical emergencies of pregnancy and labor? The American Board of Obstetrics and Gynecology has done much to educate our profession to the idea of the woman's specialist. More and more there is a tendency toward the combination of obstetrics and gynecology in the fundamental organization of departments in our medical schools. During the past few months information obtained from questionnaires and medical college catalogues indicated fifty of seventy four-year medical schools and colleges in the United States support combined departments and teach obstetrics and gynecology as one subject. Obviously, the trend of medical practice today, at least among urban populations, is toward the combined specialty of obstetrics and gynecology.

### Staff

*The "Full-Time" Staff.*—The organization of a clinical department depends on the chief. Dr. Joseph L. Baer in the opening address of the Third American Congress on Obstetrics and Gynecology said, "I am firmly convinced that heads of medical school departments, in our specialty certainly, and probably in all clinical specialties, should be seasoned clinicians who have a flair for teaching and an appreciation of research." Dr. Baer's first specification is "seasoned clinician." I would insist this is not only the first specification but also the sine qua non of a department head. Nevertheless, each of us in this room can probably remember an instance in his own medical institution where the head of some major clinical department was chosen for his research achievement—or promise—with the thought that he would learn to be a good doctor by and by.

I submit two simple, and yet profound, thoughts. "Simple" because they are obvious; "profound" because many individuals on medical college faculties don't know them, or refuse to believe: (1) Most students go to medical schools to learn to become physicians. (2) The best way to become a physician is to observe and treat sick people. The latter can be accomplished only in a well-run hospital under competent professional direction. This implies continuity of departmental treatment philosophy, techniques, and educational policies.

Much has been written concerning the part-time versus the full-time teacher, and the controversy cannot be settled in a general fashion without due consideration of local situations. No attempt will be made to settle it here. On the other hand, it is permissible to point out that the magnitude of any achievement is largely the result of expenditure of time and energy. Obviously, the mediocre man whose principal expenditure of time and energy is directed toward the development of a clinical department, can and will build larger and better than a more brilliant physician devoting most of his talents to private practice. On the other hand, when the full-time man possesses excellent capabilities and a sound and active mind, his achievement will be enormous.

Second to clinical proficiency, I believe the department head must possess

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## PRESIDENT'S ADDRESS

### The Organization and Relationships of a Department of Obstetrics and Gynecology

WILLIAM F. MENGERT, M.D., DALLAS, TEXAS

THIS address will offer certain thoughts concerning the organization and relationships of a Department of Obstetrics and Gynecology. My only justification for so doing lies in twenty years' experience and more or less intimate association, since graduation from medical school, with three such departments.

You will note that no mention has been made of separate academic departments of Obstetrics or of Gynecology, nor will there be after this paragraph. The time when medicine was divided into the groups of those who cut and those who do not has long since passed. Perhaps the technical aspects of surgery were one time so exacting and demanding as to justify concentration of training on manual skill. In some measure this is still true of the surgery of the head and thorax but not in other fields. The surgery of the female genitals requires training and skill, but any good physician with ten active fingers and ample clinical material during his residency years can learn the techniques. He does not have to be a virtuoso to acquire gynecologic operative proficiency. Far more important than polished technical skill is the knowledge of when not to operate and what not to do. Who knows this better than the man devoting his life to study of the physiology and the pathology of the female generative apparatus? Moreover, is it not absurd to attempt separation of the physiology

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NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."



If the department is large, more than one full-time professional teacher is necessary. All should enjoy the privileges accorded the chief, but scaled in proportion to rank, training, and ability.

*Visiting Staff.*—In addition to the nucleus of full-time men, a group of clinical instructors chosen from physicians in the private practice of obstetrics and gynecology in the community is invaluable. These men have much to contribute to the instruction of students and house officers. In return, a certain proportion of the clinical work should be assigned to them, but always the majority must be reserved for the resident staff. Moreover, it should be clearly understood that these part-time clinicians are men of experience and years beyond the training level. It is no part of the function of any clinical department to give part-time residency training to men engaged in the gainful practice of medicine. The function of the clinical instructor is to teach, and it is for this purpose that clinical material is made available to him. If he is not qualified by training or experience for a staff position he must be relieved of his duties. Finally, I do not believe the visiting staff should rotate in control of the service, otherwise continuity and integration of policy and technique are lost.

*Resident Staff.*—The basis of a good department of Obstetrics and Gynecology is the hospital clinic, with ample numbers of patients both in the outpatient department and on the wards. The resident service is the *heart and soul* of the clinic. The residents, working always under adequate supervision by the full-time and visiting staffs, carry the clinical load and do the bulk of the person-to-person medical student teaching. In other words, they disseminate the teachings of the senior staff. Alert, aggressive, intelligent, and curious young men are always attracted to the institution whose teaching program is coordinated and allows for upward progression. Principally, they learn from the patient, and it is precisely for that reason they are in the hospital. On the other hand, they must be properly supervised. Too little supervision is, perhaps, worse than too much, although the latter is not good. The resident must be given general directions, taught basic philosophies, and be free to work out details. Nevertheless, he must always be subject to prompt, fair, and certain criticism for obvious error. The training of the senior resident is a highly personalized affair and, except that patient care is essential, approximates the ideal of teaching through the medium of two men sitting on a log. The senior resident must be permitted to exercise judgment and perform obstetric and gynecologic operative procedures without the threatening nuisance of a hovering staff man. These are the years when he ceases to be an amateur and becomes a professional. Obviously, he will get into trouble on occasion, and some human suffering is inevitable. The surgical injuries and deaths during an eight-year period were investigated in a department of Obstetrics and Gynecology where the gynecologic operations were performed about half and half by the resident and senior staffs. Twenty residents were responsible for thirty-eight injuries and eight deaths more than were the senior staff gynecologists. The injuries were repaired and did not result in permanent disability except in one or two instances. This is not, in my opinion, expensive training per resident. In case

It may be true that love of and desire to teach must be born into a man, but it is equally true that one so favored by heritage must develop skills through experience.

Finally, the department head should be blessed with curiosity. If he possesses the desire to know, and to learn, inevitably he will impart some of this quality to his colleagues. Curiosity engenders research. In the field of research, as in any other, techniques and skills are acquired only by the "hard" way, namely experience and practice.

Recently, Walshe<sup>1</sup> wrote the following in the *Lancet* about two categories of teachers:

Thomas Lewis clearly foresaw such a danger and warned against it; but it is clear that the presence in the modern medical school of two categories of teacher, the practising consultant and the salaried academic teacher, opens the door to this disastrous dichotomy. The practising teacher is familiar in his everyday work with the individual seen against the backgrounds of his home, his family, and his work. The full tide of human needs and distresses bears down daily upon him, and the arts and techniques of medicine are his constant and exhausting preoccupation. He may cease to look beyond them.

For the cloistered academic teacher life is different. He gets his patients washed and tidied and laid out in rows in hospital wards; their importunate and exacting wives and mothers-in-law do not intrude upon his profound cogitations. No unpleasant smells or noises break in on his ordered eloquence; house-physicians and nurses wait on his bidding and tremble at his voice, and all those seeming irrelevances that are so necessary to the balanced comprehension of the patient's total situation are carefully tidied away out of his sight. He does not miss them, for he has never known them. He is rather like the florist who can arrange the plucked blooms, from which the dead leaves and dirty roots have been removed and the earwigs shaken off, into all the combinations of form and colour his fancy dictates.

This rhetorically fancy diatribe was quoted because it seems to me to suggest its own answer to the "disastrous dichotomy." Obviously, the department head must treat his own private patients. Then students cannot ignore certain of his teachings as impractical because he lives a cloistered academic life. Moreover, he should be allowed to pocket his earnings. To ask the academician to see private patients and turn the income over to the institution not only thrusts the medical school directly into the competitive practice of medicine, but also represents the worst possible form of organized prostitution.

I believe in a system which encourages, enables, and requires the so-called "full-time" chief to devote the major part of his time, effort and energy to his department. I believe he should be allowed to utilize part of his time in gainful private practice not only for its humanizing influence, but also for augmentation of salary. Any full-time professional teacher in a clinical department expects to earn less than his practitioner colleagues. On the other hand, he should not be asked to take a financial beating, and his income should be sufficient to provide for the present, old age, and the education of his children. To prevent him from going "money mad" and neglecting his responsibilities, some sort of control is desirable. This may be in the form of limitation of time, earned money, or number of patients, depending upon local conditions.

On the other hand, good residency training represents the highest type of postgraduate education, and the man receiving it could reasonably be expected to pay a tuition fee. It is impossible to strike a financial balance between what the resident might owe in lieu of a tuition fee, and what the institution owes for his services to patients. In any event, there seems to be no immediate prospect of a change in our mores. The resident will continue to be irked at receipt of a stipend totaling less than the pay of the most worthless and ignorant hospital orderly. Therefore, prior to decision to accept a residency, he must balance the value of the training he expects to receive against the extent of the personal sacrifice demanded.

### Teaching

Teaching is done on many levels in a department of Obstetrics and Gynecology, and it is difficult to say which is the most important. Nevertheless, we must never forget that the sole reason for the organization of any medical school, however far therefrom it may have departed, was to teach medical students. In general, as Findley showed some years ago, and Stander recently, obstetrics and gynecology do not receive proportionately adequate time in the medical curriculum. It is argued, of course, there is so much to be absorbed, and obstetrics is a rather prosaic sort of business anyway. Besides, baby snatching can't begin to offer the mental stimulation afforded by the intricacies of medicine and surgery. Be that as it may, the obstetrician has an unanswerable argument. There must, and will, be babies and we don't want our women to die during the birth process. The remarkable decrease in the maternal mortality rate of the United States since 1929 should be ample testimony to the importance of the teaching of obstetrics to medical students. Many rural general practices are built upon obstetrics, since the young prospective mother tends to choose a young physician so that her family may grow with him. The general practitioner not only is delivering the majority of our women, but will continue to do so for many years to come. For this reason alone, the medical student must receive ample instruction in the fundamentals of obstetrics.

Our teaching of obstetrics and gynecology is integrated throughout the didactic and ward classes, and begins as soon as possible after the student matriculates into medical school. During his preclinical courses he is introduced to patients whenever possible in order to illustrate some of the abstract things he is learning. During the second-year course in general physical diagnosis, the specialized diagnostic techniques of obstetrics and gynecology are taught. Current trends are entirely away from the lecture as a medium of medical school teaching. Everywhere, we hear the cry to abandon the lecture and throw the student into the out-clinic and wards, there to sink or swim. There can be no doubt that in the past there were too many lectures. There can also be no doubt that the didactic lecture is abused. If the content can be read in a current text, the lecture may be a waste of the student's time. On the other hand, a well-organized lecture can save untold hours of student effort, by plac-

you do not agree, think of the financially eager young graduate, fresh from an unsupervised internship and impatient to begin cutting. He acquires surgical training without supervision on private patients and is paid for so doing. Unfortunately, we can only guess at the frightfulness of his records, if he keeps them. John B. Deaver used to say, "Graveyards are filled with the mistakes of young surgeons." Contrast this hit-or-miss acquisition of knowledge and skill with the coordinated training afforded by a supervised residency. We can rest assured that during the latter no graveyards are filled, although an occasional patient may die.

A good residency program must allow for frequent formal conferences, including mortality, pathology, clinical case presentations, reports of research and of reading. It should also stimulate interest in some basic science. When a resident exhibits interest, provision must be made for research in one of the basic science departments. There should be a sufficient number of residents so that each will have some excess of time above that required for the routine hospital ward and record work, and medical student instruction. Each resident must have opportunity for reading, thinking, and some sort of investigative endeavor. When routine matters constantly push the resident to the limit of physical endurance, the value of his training inevitably decreases.

How long should the residency years last? The American Board of Obstetrics and Gynecology has decreed a minimum of three years after the internship. Certainly, we will all agree this is the least possible time required to impart the fundamentals of our specialty. Also, it is entirely inadequate to train a teacher. On the other hand, undue extension of residency training to seven or eight years is absurd. At the present time, most of our residents are medical G.I.'s. They have devoted three to five years to service for the nation and are understandably anxious to start practice. Finally, the length of the residency training will depend, to some extent, on the community need for specialists. Where the need is not acute, the length of service may be increased.

At the present time there is an ample supply of excellently taught young men, eager to undertake the necessary years of resident training. It is impossible to say how long this situation, intensified by the post-war demand, will continue and when it will become necessary to offer financial inducements to prospective residents. At this point, perhaps a brief recapitulation of the financial aspects of residency training may be in order. Most residency services provide room, board, and laundry and pay stipends sufficient only to buy the bare necessities of life for a single man. Almost none of them makes provision for wife or family. In consequence, the prospective resident must either delay marriage or possess an independent income. Many excellent but impecunious young graduate physicians thus are lost to this and to other specialties. In this connection, we must also remember that residency training is the "grade school" in the training program of the medical college professor. If we desire good teachers, we must have good residents. It is true that compromises can be made, and some men struggle through a residency on phenomenally small incomes. This can, however, be overdone and the consequent pauperizing of the young physician and his wife may produce irreparable psychic trauma.

duties, and he is not entitled to a credit line for so doing. I do not believe his name should be attached to any paper unless he contributed ideas or actual labor over and above the composition of the text and arrangement of the data.

### Budget

Finally, the question arises, what does this program cost? Certainly, the budget of the Department of Obstetrics and Gynecology should be on a par with that of the other major departments. Unfortunately, this is not always the case. It is difficult to make any generalized statement regarding budget, because conditions vary with the school. On the other hand, it is possible to venture the belief that such a program, exclusive of the hospital and residency service, cannot be supported on an annual budget less than thirty thousand dollars. This sum represents the minimum budget of a small department. With large departments utilizing the services of a number of full-time men and research fellows, the budget must be proportionately increased. Although research moneys often can be obtained from private sources, and assistance with teaching programs from maternal and child health funds, the medical school must be prepared to finance the minimum budget.

Time does not permit discussion of many other phases of the complex activities of a major full-time clinical department. My object today was the presentation of personal ideas developed through years of intimate observation of several full-time university departments of obstetrics and gynecology.

### Reference

1. Walshe, F. M. R.: *Lancet* 2: 817 (Dec. 6), 1947. Quoted in *J. A. M. A.* 137: 1190 (July 31), 1948.

ing proper emphasis upon the subject material. Let us curtail the number, but not abandon, the didactic lecture.

Other types of postgraduate education, in addition to residency training, include the refresher teaching of general practitioners, and the preparation of young specialists for examination.

The influence of any university must be felt beyond the walls. Nowhere is this more evident than in continuation teaching of physicians in the vicinity. There are many methods of continuation teaching, including: extension lectures and courses, the return to the parent university of individual physicians or groups, informally or for a stated course, and participation of those who care in the regular conferences and clinics of the department. Special programs held by the department at the medical school and hospital should be planned for men in general practice, and advertised in an attractive manner. With each of these different methods of postgraduate teaching, emphasis must be placed upon clinical obstetrics and gynecology. You and I may be interested in the academic aspects of bony pelvic classification, or the mechanisms of production of pelvic pain, but the practicing physician wants to know, will this baby pass through, or is the pelvic pain of such origin and intensity as to warrant operation.

I believe also the local medical school should offer the younger practicing specialists contemplating board examination the facilities of laboratories, libraries, and hospital clinics. In certain instances it should provide special courses adapted to their needs.

### Research

Research is necessary to any progressive department, but what kind? It is given to few men, or few institutions, to make fundamental, earth-shaking discoveries. Moreover, basic laboratory research requires elaborate techniques, costly apparatus, and specialized skills far beyond the experience and training of even a good resident. On the other hand, any man with sufficient imagination can become aware of a small problem and devise simple experiments to test his views. It seems to me the purpose of departmental research should be to inculcate into the resident the desire and the initiative to satisfy some of the questions arising in the practice of the specialty. This implies stimulation of each resident to conduct some simple investigation, however small. I do not believe it is our purpose to make research workers of our residents, although any man with a bent in that direction must be afforded opportunity. Fundamental research programs have their place in the large well-endowed departments of older universities. Even here, however, I am dubious of results obtained on lower animals. The reproductive physiology of the human being differs so much from that of the lower animals, that experimental results on less than a primate basis are often unreliable.

I cannot leave this section on research without a few words on the authorship of papers. Articles bearing the imprint of the department must be edited and approved by the chairman. This constitutes one of his major

center from which most of the embryo develops. Extending anteriorly ventral to the neural tube is the notochord, which is the forerunner of the axial skeleton. As the axial skeleton develops, the notochord becomes a minute canal in the center of the vertebra. The center of the nucleus pulposus is a remnant of the notochord. For a short time there is a connection between the neural tube and the primitive gut of the embryo, which is known as the "neurenteric canal." Early in development this canal becomes obliterated.

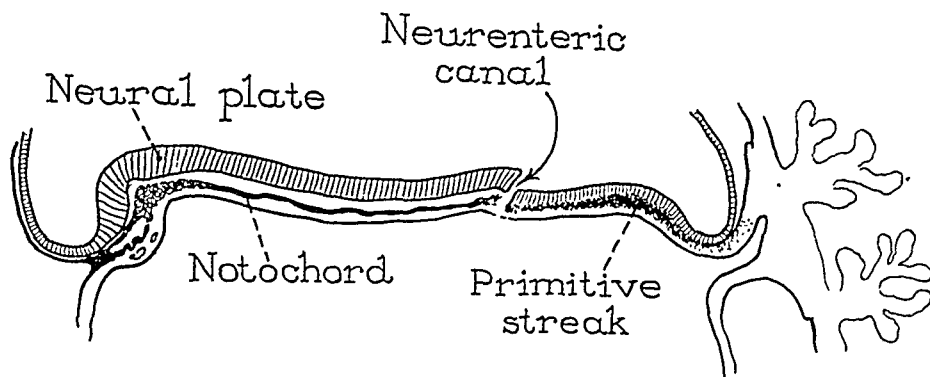


Fig. 1.—Sagittal section of an early embryo, showing the primitive streak, the neurenteric canal, and the notochord.

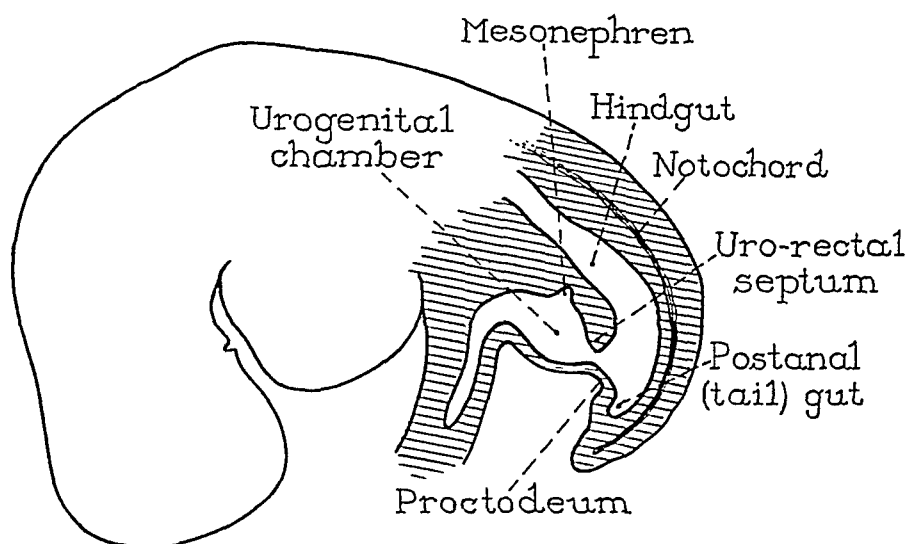


Fig. 2.—Sagittal section of an early embryo, showing the development of the hindgut, the proctodeum, and the postanal hindgut.

As the folding process of the caudal end of the embryo proceeds both laterally and ventrally, the primitive gut can be differentiated into the hindgut and the midgut, connected to the embryonic cavity by the posterior intestinal portal (Fig. 2). There is an invagination of the surface of the body which makes contact with the cloaca (dilated portion of the hindgut), forming the proctodeum or primitive anus. The proctodeum is somewhat anterior to the terminal portion of the hindgut. This portion of the hindgut is called the "postanal hindgut," which later becomes obliterated. The cloaca becomes divided into a posterior portion, which later becomes the rectum, and an anterior portion, which subsequently becomes divided into three parts to form the urachus, the bladder, and the vestibule of the vagina in the female. From this anterior portion of the cloaca spring the renal pelvis and ureter, and

## EXTRAGENITAL PELVIC TUMORS IN WOMEN\*

SIM B. LOVELADY, M.D., AND MALCOLM B. DOCKERTY, M.D., ROCHESTER, MINN.

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PELVIC tumors of extragenital origin are of interest to the obstetrician, since they occasionally obstruct the birth canal at the time of delivery. These tumors are of interest to the gynecologist, since they present problems in differential diagnosis and surgical management. To the pathologist they present a variety of gross and microscopic pictures rarely encountered in any other tissue. Such tumors often simulate tumors of the ovary and fibroid tumors of the uterus. They may be found to arise from the pelvic bones and their surrounding soft parts, from nerve tissue or from some congenital anomaly. They may be freely movable or adherent to the anterior sacral wall. This paper is a clinical and pathologic study of these tumors.

Although the literature contains no comprehensive review of extragenital pelvic tumors in women since Lever's report in 1843,<sup>1</sup> there are numerous articles reporting on isolated examples and small series of these tumors. Thus Middeldorpf in 1885<sup>2</sup> called attention to the presacral group of teratomas arising from the postanal hindgut. Cragin in 1893<sup>3</sup> emphasized the importance of ectopic pelvic kidneys in the matter of obstructing the birth canal. Utter and Bates<sup>4</sup> and Hundling<sup>5</sup> focused attention on the neurogenic group of presacral tumors; namely, the neurofibromas, ganglioneuromas and ependymal-cell gliomas. Fletcher, Woltman, and Adson<sup>6</sup> found that presacral chordomas as a group were frequently confused with chondromas. Cases of vesical tumors with presacral extension were the subject of a paper by Sheffery<sup>7</sup> in 1946, while Banner, Hunt, and Dixon<sup>8</sup> observed similar extension of a rectal carcinoma. These and numerous other excellent articles<sup>9-22</sup> formed a substantial background for our study of this interesting subject and have made possible a comparison of our own findings with those of others interested in the field.

### Embryology of the Sacrococcygeal Region

Various types of tumors may arise from the sacrococcygeal region and present anteriorly in the pelvic cavity. Such tumors may not seem so unusual when one stops to consider the complexity of the embryologic development of this part of the body.

The textbooks on embryology state that early in development three primary germ layers are detectable, the ectoderm, the entoderm, and the mesoderm. From these structures the various organ systems of the body develop.

As seen in Fig. 1, there appears a thickening near the caudal end of the embryonic region. This longitudinal cell mass is known as the "primitive streak." There is a mass of cells at the anterior end of the primitive streak called "Hensen's node." For a time the primitive streak is the growth

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Ectopic pelvic kidneys in a sense become tumors when located below the brim of the pelvis. We wish to include a brief discussion of fifty-six cases of ectopic pelvic kidneys in addition to the seventy-one cases of extragenital tumors in the strict sense. More often than one might suspect, the gynecologist or the general surgeon has been somewhat chagrined on opening the abdomen to find that a supposed pelvic tumor was a functioning pelvic kidney. In twenty-seven of these fifty-six cases the diagnosis of ectopic pelvic kidney was not made prior to operation, but in many of these cases operation was performed before the advent of intravenous urography. These kidneys are thought to be asymptomatic unless they produce symptoms from pressure due to infection and hydronephrosis. Whether a normally functioning pelvic kidney can cause symptoms is a question for the urologist, but we have all encountered cases in which there was reasonably good evidence that they can produce pain. Such pelvic kidneys can produce dystocia but in many cases reviewed by us there was a history of the birth of several children without difficulty. If the question of dystocia does become a problem, cesarean section is the treatment of choice. In these fifty-six cases there was only one which complicated pregnancy. In ten (18 per cent) there was some associated defect in the female genital tract such as congenital absence of the vagina, bicornate uterus, and so forth. We are not suggesting that an excretory urogram be made in every case of pelvic tumor but it should be advised in every case of suspected presacral retroperitoneal pelvic tumor.

Figure 3, *a* shows an anterior meningocele pushing the rectum and pelvic structures forward. Figure 3, *b* shows a presacral neurofibroma complicating pregnancy.

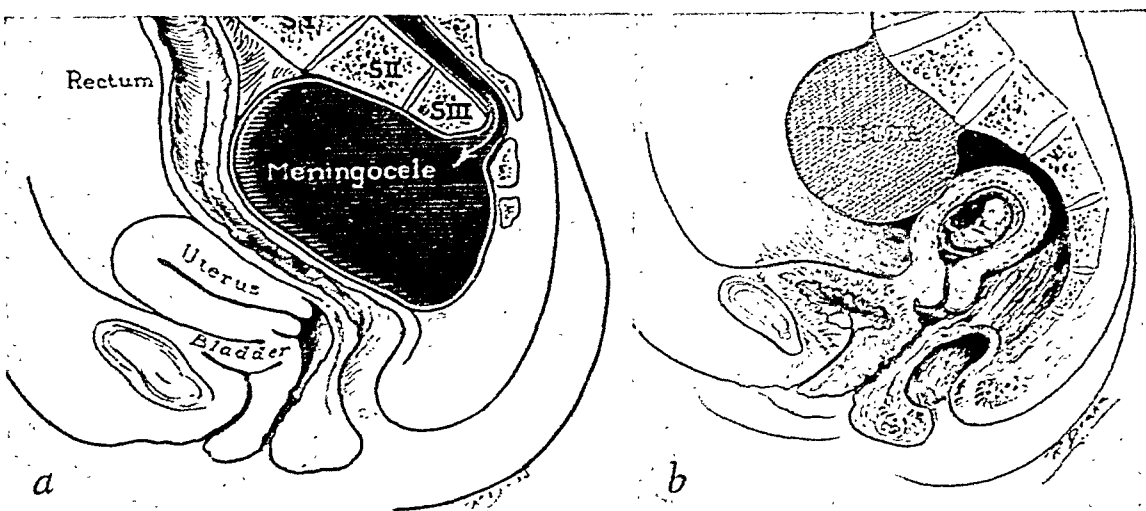


Fig. 3.—*a*, Anterior sacral meningocele. *b*, Presacral neurofibroma complicating pregnancy. (From De Voe, Lovelady, Dockerty, and Gray.<sup>20</sup>)

### Pathology

**Materials and Methods.**—Surgically excised material or suitably prepared slides were available for pathologic review in sixty of the 127 cases studied. In the remainder either no tissue had been removed for diagnosis or both tissues and slides had been lost or destroyed. All of the gross specimens had been preserved in 10 per cent formalin, and these were secured and studied carefully for diagnostic features such as degree of encapsulation, the presence

accordingly it is not surprising that anomalies in position of the kidneys can be explained on this embryologic basis. Thus we see how numerous structures in this region of complex development may become the sites of origin of a wide variety of tumors.

### Present Study

This review covers a period of thirty-eight years, from 1910 through 1947. Some of the cases presented in this study have been included in other series of cases reported by other authors from the Mayo Clinic. We reviewed 127 case histories from the files of the clinic of extragenital pelvic tumors occurring in women. Fifty-six of these were ectopic pelvic kidneys diagnosed by intravenous urography and surgical exploration. In eleven cases pathologic specimens were not available for study. In sixty cases the pathologic specimens were reviewed. These tumors may occur at any age. We were particularly interested in those patients in the child-bearing age in whom the tumor complicated pregnancy. The tumors which presented some problem of differential diagnosis in the female pelvis by encroaching on the birth canal were included. Table I shows the division of the cases into three groups according to age: (1) from birth to puberty, (2) the reproductive period, and (3) the postmenopausal period, as well as the pathologic division into four categories: (1) congenital anomalies, (2) neurogenic tumors, (3) bone tumors, and (4) miscellaneous group. In ten cases the extragenital tumor complicated pregnancy. The congenital group formed the bulk of the series with seventy-two cases. Tumors of the bladder and rectum have not been included in this review but the gynecologist should remember that tumors of these organs may simulate ovarian tumors and should be kept in mind in the differential diagnosis of pelvic neoplasms.

TABLE I. EXTRAGENITAL PELVIC TUMORS OF WOMEN\*

TYPE OF TUMOR	AGE GROUPS			COMPLICATING PREGNANCY
	BIRTH TO PUBERTY	REPRODUCTIVE PERIOD	POST-MENOPAUSE	
<i>Congenital Anomalies.</i> —				
Ectopic pelvic kidney			1	1
Specimen examined		42	13	
No specimen		8	1	
Teratomas	5	2		1
Meningocele				
<i>Neurogenic Tumors.</i> —				
Neurofibroma		6		3
Ependymal-cell glioma			2	
Ganglioneuroma	2	1		1
Ependymblastoma			1	
<i>Bone Tumors.</i> —				
Benign giant-cell tumor of bone	1	4		
Cartilaginous and osteocartilaginous		4	3	1
Osteogenic sarcoma		1	1	
Ewing's tumor		1		
Chordoma		1	2	
<i>Miscellaneous Group.</i> —				
Myogenic group		4		1
Fibroma		1		
Inflammatory		2	3	1
Metastatic carcinoma		2	2	1
Unclassified		5	6	

\*In ten cases the tumor was inoperable and no specimen could be obtained. In one case the anterior sacral meningocele sac was not removed.

microscopically showed a preponderance of ectodermal derivatives (Fig. 4, *b*). One of the patients was a girl, aged 7 years; the remaining five were adults. In one the existence of the tumor had been known since birth and in another from the age of 8 years. Four of the tumors were infected (Fig. 3, *c*) and in two of these instances one or more operations had been performed in unsuccessful attempts to drain "abscess" cavities. The sizes ranged from 6 cm. in diameter for the smallest to 16 by 11 by 7 cm. for the largest. Three were encapsulated and removable without difficulty while three were quite adherent as a result of infection or previous operative intervention. Two of these were successfully ablated while in the third it was apparently impossible to obtain all of the lining and the patient continued to have trouble.

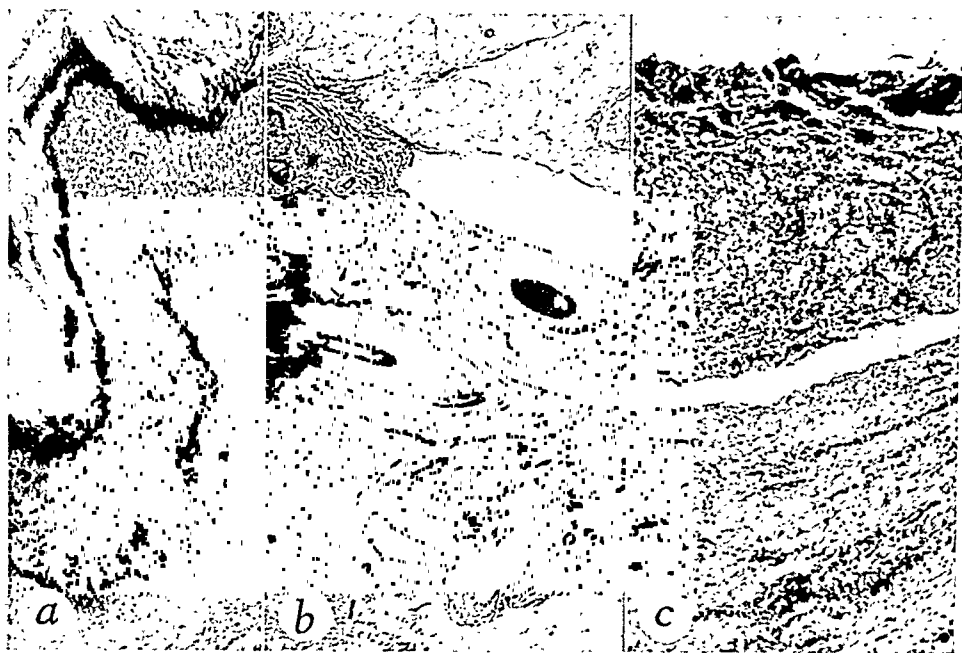


Fig. 4.—*a*, Simple epidermoid cyst. The lining is stratified squamous epithelium and there are no specialized skin structures (hematoxylin and eosin  $\times 40$ ).

*b*, Dermoid cyst showing skin derivatives, brain tissue, smooth muscle and fat (hematoxylin and eosin  $\times 40$ ).

*c*, Infected presacral dermoid cyst showing masses of foam cells (hematoxylin and eosin  $\times 60$ ).

Microscopically all of the growths exhibited the presence of entodermal and mesodermal as well as ectodermal derivatives and all were benign. Infection was a marked feature in four cases with abscess formation and granulomatous reactions with foam cells (Fig. 4, *c*) and giant cells.

3. *Complex teratoma* (5 cases): Included under this subheading were solid and semi-solid tumors of teratomatous composition which microscopically did not reveal any preponderance of ectodermal structures.

Four of the patients were infants whose ages varied from 4 months to 3½ years, and whose trouble for the most part dated from birth. One patient was an adult with relatively short clinical history. In contrast to the "dermoid" group none showed evidences of infection. The tumors were in general large with diameters ranging from 10 to 25 cm. All were fairly well encapsulated and except for the malignant example, were apparently removable in toto.

Microscopically, the tissue complexity was remarkable. One tumor demonstrated an unusual type of malignancy in that it consisted entirely of neoplastic thyroid tissue (Fig. 5, *a*). In spite of subtotal surgical removal augmented by the application of radium needles the patient died three years later from symptoms which suggested local recurrence and pos-

of hair and sebaceous material, evidences of fatty degeneration such as one sees in neurofibromas, the gelatinous consistency of chondromas, chordomas, and giant-cell tumors, and so forth. Representative blocks were then cut from each of the lesions, these were placed in bottles of fresh 10 per cent formalin, sectioned on a freezing microtome and stained routinely with hematoxylin and eosin. Original slides were also secured and added to the collection, which amounted to several hundred sections available for microscopic study. The large group of ectopic kidneys we readily accepted without microscopic confirmation but the only other "exception" was the inclusion of one typical anterior sacral meningocele which the neurosurgeon ligated but did not remove.

Preliminary microscopic survey disclosed that the various individual lesions could be conveniently grouped into the following four categories: (1) congenital lesions, (2) neurogenic lesions, (3) osseous lesions, and (4) a miscellaneous group embracing various other soft-tissue tumors and inflammatory masses.

## Findings.—

### *I. The Congenital Group.—*

This was the largest group, accounting for more than 50 per cent of the tumors.\* It contained three distinct subdivisions: (a) congenital ectopic pelvic kidneys, fifty-six cases; (b) anterior sacral meningocele, two cases; (c) teratomas (including epidermoid cysts, dermoid cysts, and more complex teratomas), fourteen cases.

(a) *The Renal Subgroup.*—One of these 56 ectopic kidneys was removed because of hydronephrosis and pyelonephritis. It is surprising that the group did not manifest more in the way of pathologic change but as a consequence the condition becomes more of a problem to the clinician, who must always consider it in any differential diagnosis of presacral tumors. The high incidence of associated congenital anomalies of the reproductive organs should be mentioned.

(b) *Anterior Sacral Meningocele.*—This is a rare lesion with only about twenty-five cases recorded in the literature. In one of our two patients (both adults) the cyst measured 10 cm. in diameter, the pedicle of the herniation passed through a defect in the upper anterior portion of the sacrum, and the latter had the typical scimitar deformity so commonly associated with the condition. In the second case there was dilatation of the sacral canal and the herniation (4 cm. in diameter) was through one of the sacral foramina. In this case the presence of arachnoidal cells and glial tissue was readily identified. Because this lesion connects with the subarachnoid space, accidental contamination is likely to lead to disastrous results and the operative mortality rate in the past has been 50 per cent.

(c) *The Teratoma Group.*—Fourteen cases comprised this subdivision, the second largest single aggregation. Three subgroups could be readily distinguished.

1. *Epidermoid cyst* (3 cases): The tumors were characterized by being unilocular grossly, and microscopically exhibiting only a stratified squamous epithelial lining with no skin derivatives and no evidence of entodermal or mesodermal components (Fig. 4, a). All three patients were adults. One had no symptoms referable to the tumor and one had discovered it three years previously while taking an enema. In the third patient the tumor had become infected and had ruptured and drained. The largest tumor measured 10 by 7 by 4 cm. and the other two measured 3 cm. each in diameter. Two were encapsulated and readily enucleated. The infected tumor was adherent.

2. *Dermoid cyst* (6 cases): Under this heading were included unilocular and multilocular cystic tumors which grossly were filled with sebaceous material or hair or both and which

\*Used in a clinical sense to designate "palpable swelling."

another patient the adherence to surrounding tissues of a large pelvic neurofibroma was responsible for such serious hemorrhage at removal that the patient died shortly after operation.

Microscopically, nuclear palisading was the outstanding feature (Fig. 5, *b*). No mitotic figures were observed in any of the sections and accordingly all of the tumors were adjudged to be benign.

(*b*) *Ganglioneuroma* (3 cases).—Two of these tumors occurred in children, aged 5 and 5½ years, respectively. The third patient was an adult. Bohrer and Lincoln,<sup>23</sup> expressing the opinion that this tumor is rare among children, noted, however, that in most of the reported instances the patients have been less than 30 years of age. The two children exhibited signs and symptoms of chronic intestinal obstruction from large tumors which were surgically irremovable. In each instance a biopsy was made and roentgen therapy was instituted. One of these patients was living when this paper was written, seven years postoperatively, the growth of the tumor having been arrested or at least slowed down; the other died four years after the course of treatment. In the third patient a poorly encapsulated ganglioneuroma was removed piecemeal from the right side of the pelvis after dissection from the obturator nerve and the iliac vessels.

Ganglioneuromas may arise inside or outside the central nervous system, from any situation wherein ganglion cells are found. The retroperitoneal, presacral, and mediastinal examples most frequently spring from sympathetic nerve plexuses and often apparently from multiple centers. It is thus that we explain the broad bases of attachment and the frequent (50 per cent) nonresectability of this rare tumor, which, paradoxically enough, is nearly always benign. Even the occasional malignant examples, which are usually found in children and which are malignant by virtue of a neuroblastic cellular component, are irremovable, not so much because of their "cancerous" nature per se as because of this selfsame picture of multicentric origin.

Microscopically all three tumors demonstrated the admixture of ganglion cells, satellite cells, and varying proportions of myelinated and nonmyelinated nerve fibrils (Fig. 5, *c* and *d*). All of the elements appeared reasonably mature and no embryonic neuroblasts were observed. It is possible that more material from the two inoperable tumors would have furnished us with positive evidence for malignancy in these two cases.

(*c*) *Ependymal-Cell Glioma* (3 Cases).—All of the patients were adults whose ages were 45, 56, and 65 years, respectively. The symptoms, measured in terms of years, were in two instances referable to severe nerve-root irritation featuring pelvic and sciatic pain and in the third to neurogenic sphincteric vesical and rectal dysfunction with incontinence. All three tumors were large with marked expansion and destruction of the sacrum and growth into the surrounding soft parts. Two patients stated that they had had previous operations for their trouble. The treatment at the clinic in these two instances consisted in partial removal of recurrent tumor masses and insertion of radium needles. Both of these patients died, three and four years, respectively, after operation. Our third patient had a clinical diagnosis of uterine fibromyomas with compression of the rectum. At the time of hysterectomy the surgeon noted that one of the "supposed" fibroids appeared to be springing mushroom-like from a stalk of tumor tissue which protruded through one of the anterior sacral foramina (Fig. 6, *a*). A fresh frozen section disclosed ependymoma, grade 2, and one of our neurosurgeons, who was called into the operating room, confirmed origin of the tumor from the interior of the sacrum. The growth, which was encapsulated and 8 cm. in diameter, was resected from its stalk and removed along with the uterus, Fallopian tubes, and ovaries. The patient was advised to return in three months for treatment of the intrasacral component of the ependymoma. She did not follow this advice and at her last report she was confined to a "mental" institution.

Ordinarily classified as a type of intramedullary glioma (and comprising 60 per cent of the spinal-cord group of gliomas) it is indeed surprising that the majority of these neoplasms arise from that filamentous and grossly unimportant-looking segment of the spinal cord known as the "cauda equina." Yet it is this very fact plus anatomic peculiarities of the sacrum which feature the almost unheard-of circumstance of a glioma extending outside

sibly metastasis. We have not encountered another such presacral tumor in the literature but are familiar with its ovarian counterpart, the malignant strumal tumor, and accordingly have placed the same histogenetic interpretation on our case.

## II. The Neurogenic Group.—

All of our dermoids and complex teratomas revealed the presence of neurogenic elements, but twelve additional tumors were entirely of neurogenic origin and composition. This group of twelve tumors lent itself conveniently to subdivision into three categories: neurofibromas, ganglioneuromas, and ependymomas:

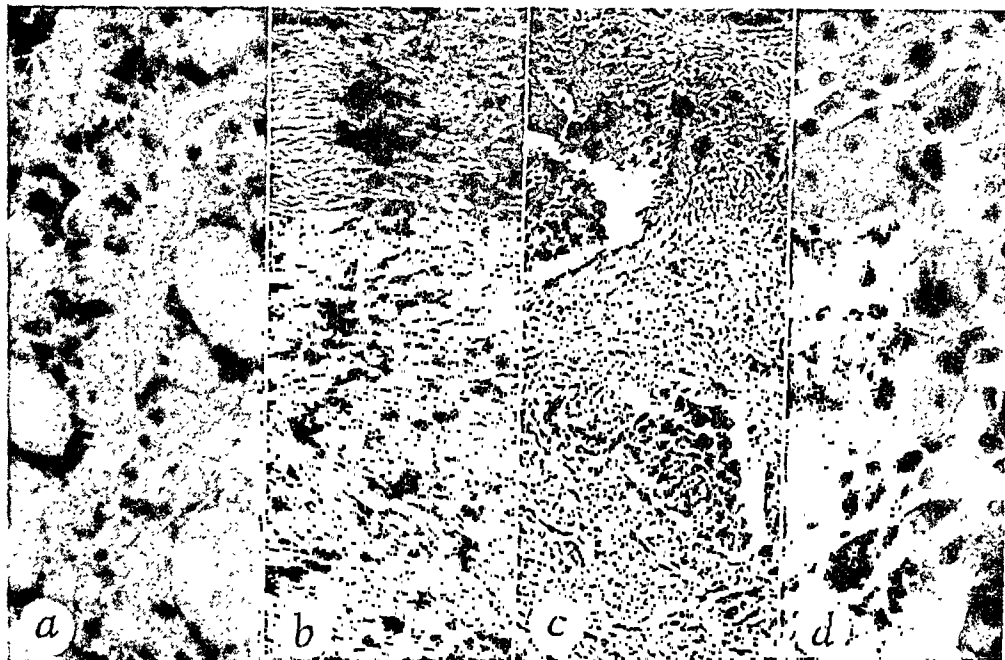


Fig. 5.—*a*, Malignant complex teratoma showing the most unusual picture of adenocarcinoma, grade 1 (Broders' method), involving the thyroid component of the tumor (hematoxylin and eosin  $\times 360$ ).

*b*, Presacral neurofibroma illustrating the spindle cells and their palisaded nuclei (hematoxylin and eosin  $\times 215$ ).

*c*, Presacral ganglioneuroma showing masses of ganglion cells and nerve fibrils (hematoxylin and eosin  $\times 60$ ).

*d*, Details of ganglion cells. Note surrounding dark-staining satellite elements (hematoxylin and eosin  $\times 275$ ).

(a) *Neurofibroma* (6 Cases).—These tumors all arose in young women whose ages ranged from 17 to 35 years. None exhibited features of von Recklinghausen's disease. In two the tumors were accidentally discovered, since they were symptomless. In several there was pain. In one patient the tumor was discovered and removed early in pregnancy, in another the tumor interfered with delivery and in another there was a history of difficult labor three years previously. Two arose from one or other of the obturator nerves and one had its origin from an anterior sacral nerve. In the remainder it was difficult to ascertain the nerve of origin. The tumors averaged about 9 cm. in diameter, three being encapsulated and yellow. Two of the specimens were large, each measuring 20 cm. in diameter. One neoplasm was dumbbell in appearance, protruding through the left obturator foramen, exhibiting large intrapelvic and extrapelvic portions and making difficult the operative removal by stage procedures. Another patient, believed originally to present a similar situation, gave a history of having undergone two operative attempts at removal. The residual mass was very difficult to enucleate and the patient is believed to be now suffering from recurrence. In still

### III. The Osseous Lesions.—

This was the second largest of the main groups, comprising eighteen lesions which we subdivided into the following five categories.

(a) *Chondroma and Osteochondroma, Benign and Malignant* (7 Cases).—In this group it was found possible to subdivide the neoplasms into those which were of essentially pure cartilaginous composition (enchondromatous tumors, 4 cases) and those which exhibited a mixture of bone and cartilage (ecchondromas, 3 cases). There is evidence in the literature<sup>24</sup> that the former group of tumors tend to be multiple, to be centrally located in bony substance near old epiphyseal centers and to be occasionally malignant. The ecchondromas or true osteochondromas are supposedly subperiosteal in location and partake more of the characteristics of an exostosis (traumatic?) than of a true neoplasm.

None of our four patients with enchondromatous tumors showed evidence of multiple chondromatosis, their tumors all being solitary. All four patients were adults with ages ranging from 35 to 62 years. Pelvic pain, often with sciatic extension, and the presence of a tumor combined with symptoms referable to pressure on pelvic viscera were the predominant symptoms, which varied in duration from six months to four years. One patient with a chondrosarcoma, grade 1, stated that the tumor had interfered with delivery of her last baby. One of the four patients had undergone operation previously and had come to the clinic for treatment of recurrences. This patient, as well as the remaining three, died within five years from effects of subsequent recurrences and in one case from uterine vesical and omental metastasis. Pelvic chondromas and chondrosarcomas are prone to recur even when the direction of growth is outward, and the only hope of cure lies in complete extirpation at the time of the first operation, often by a procedure of the order of magnitude of a hind-quarter amputation.<sup>25</sup> The propensity to recur of benign tumors of this type is too often related to the "spilling" of a few tumor cells during the performance of a tissue-saving operation. Roentgen therapy is next to useless in the prevention of these recurrences. All of the tumors were large. Two originated from the left ilium, one from the right ilium, and one from the right innominate bone.

Microscopically, one of our tumors was benign. Three of the tumors were chondrosarcomas, grade 1, on the basis of increased cellularity, nuclear hyperchromatism and, most important, mitotic figures (Fig. 7, a). In all three chondrosarcomas it was evident microscopically that "malignancy" had been superimposed on a benign process.

Our three patients with osteochondromas (ecchondromas) were all adults whose ages were 18, 25, and 54 years, respectively. One of the tumors was asymptomatic, being discovered during routine exploration of the pelvis at cholecystectomy, and another was found during investigation for the cause of obstructed labor. The third patient noticed the slow development of a firm tumor after an injury to the pelvis. The growth gradually expanded to the point where it interfered with walking. Two of the tumors arose from the right os pubis; they were small (8 cm. and 3 cm. in diameter, respectively) and they were removed in toto. No recurrence was noted. The third patient had a tumor, estimated to measure 25 cm. in diameter, which, she stated, had been partially removed three years previously. The residual tumor mass was considered irremovable but enough was chiseled away to allow for motion of the leg. She died from the effects of postoperative pulmonary embolism, and permission for necropsy was withheld.

Microscopically, the composition of these three tumors was that of a mixture of bone and cartilage, both elements varying in proportion from slide to slide and both apparently being adult and benign (Fig. 7, b).

(b) *Osteogenic Sarcoma* (2 Cases).—Two of our patients, 18 and 57 years of age, respectively, had malignant tumors arising from bony mesenchyme and accordingly designated osteogenic sarcoma on the basis of this interpretation.\* Pain had developed in the left hip of the younger patient after an injury six months prior to admission. A lump had been

\*Strictly speaking, the designation "osteogenic sarcoma" should mean a bone-producing type of sarcoma.

the central nervous system and presenting in the pelvis. In these cases, therefore, one must always remember that in addition to the pelvic soft-tissue component, there is also a large and perhaps more serious component involving the spinal canal of the sacrum. The ideal treatment, namely, complete surgical extirpation of both, can rarely be accomplished.

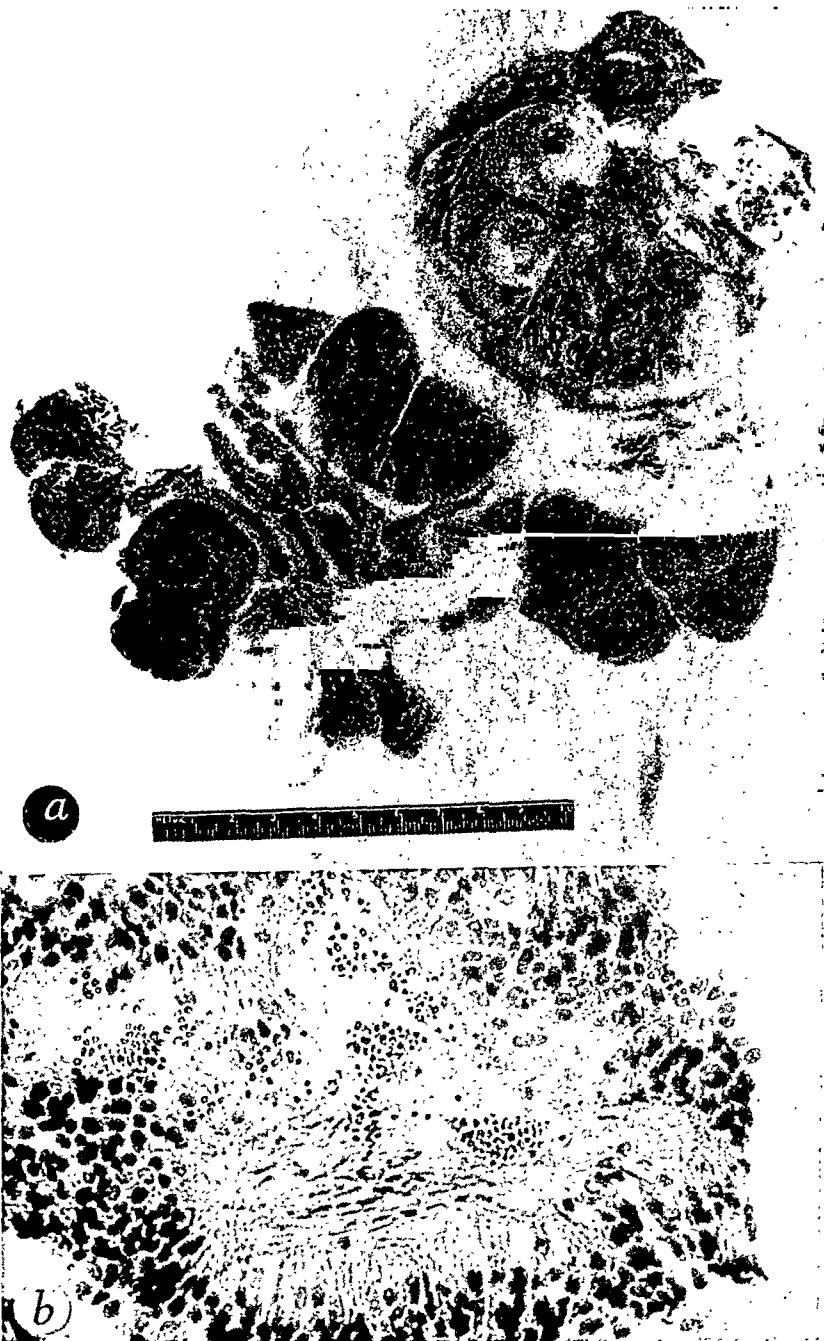


Fig. 6.—*a*, Large presacral ependymoma associated with uterine fibromyomas. The surface of the tumor is smooth except in the region of the pedicle.

*b*, The ependymal cells with their long processes are arranged in rosette fashion around a blood vessel (hematoxylin and eosin  $\times 190$ ).

The microscopic appearance of each of our tumors was typical, with spindle cells arranged radially around clear spaces representing abortive "central canals" and blood vessels (Fig. 6, *b*) or, again, about felted fibrillar masses, the processes of the ependymal cells. Mitotic figures were not observed and the tumors were judged to be of a low order of malignancy only.



(c) *Ewing's Tumor (Angio-Endothelioma of Bone)* (1 Case).—Our 19-year-old patient who exhibited this condition had suffered for six months from fever and from pain in the right hip. The pain was worse at night than during the day. She stated that her pelvic tumor had been discovered during appendectomy. For two months she had been bedridden with much pain and marked limitation of movement of her right thigh, which was semi-fixed in the position of flexion. The tumor, which apparently arose from the crest of the right ilium, was large, fixed, and irremovable. Biopsy material showed angio-endothelioma (Ewing's tumor), grade 4. After a course of roentgen therapy the patient died from the effects of "generalized sarcomatosis."

(d) *Giant-Cell Tumor* (5 Cases).—One of our patients with this condition was a 12-year-old girl, the other four being adults whose ages ranged from 19 to 57 years. Duration of symptoms was short, being less than ten months in all except one patient. Injury appeared to play a possible etiologic role in one patient only. The tumors were all sacral in origin and, as might be expected, produced symptoms referable to pressure on various parietal and visceral nerves; three patients noted extension of pain down the legs. Two had difficulty in walking resulting from invasion of soft tissue and pressure by the tumor on motor nerves. One complained of "cystitis" and two had difficulty with "bowel control." By roentgenographic examination or at operation it was ascertained that the tumors had destroyed small or large portions of the sacrum. In one instance the tumor had grown upward extensively into the subarachnoid space; in another the tumor had infiltrated extrasacally into the leaves of the mesentery of the sigmoid. Perforation of the sacrum posteriorly as well as anteriorly was noted in still another instance. In two patients it was possible for the surgeon to effect a semicomplete removal of poorly encapsulated, soft, reddish, friable tumor tissue. One of these patients was treated postoperatively with Coley's toxins. She survived for twenty-four years, eventually dying from conditions unrelated to her original tumor. In the second patient roentgen therapy was given after removal of a 15 cm. giant-cell tumor and the patient was living when this paper was written, twenty-seven years later. There was one operative death in the group, the cause of death being uncontrollable hemorrhage. This occurred in the case in which at necropsy extension of tumor in the subarachnoid space was observed. The remaining two patients had tumors that were too extensive for anything except biopsy and roentgen therapy. Both died within five years from the development of their trouble, one as a result of spinal extension of the tumor and its attendant neurologic complications.

Microscopically, the composition of multinucleated giant cells in great numbers and a stroma of spindle cells was unmistakably typical of giant-cell tumor (Fig. 8, a). Malignancy in this group of tumors runs an incidence of about 3 per cent and it is always exhibited in the stroma and not in the giant cells. The criterion for its presence is the demonstration of pathologic or atypical mitotic figures in the stromal cells, and the nature of the change is therefore basically fibrosarcomatous.<sup>27</sup> Although one of the tumors had originally been pronounced malignant, we were unable on review of the tissue and slides to confirm this diagnosis. Notwithstanding the fatal clinical outcome in several of the cases we therefore designated all the tumors as being microscopically benign.\*

(e) *Chordoma and Chordoblastoma* (3 Cases).—Chordomas arise from remnants of the embryonic notochord and they are accordingly not truly of osseous derivation. However, since pelvic chordomas spring from the sacrum, it becomes convenient to classify them with our group of bone tumors. Seventy per cent of chordomatous tumors arise from the sacrum and the majority of the remainder spring from the basisphenoid and basioccipital regions. It is surprising that the spinal column proper furnishes such a small number of chordomas, considering the fact that notochordal tissue is native to all the intervertebral disks. Chordomas are rare tumors, occur for the most part in adults and are only half as common in men as in women. They furnish us an example of a paradox in pathology in that, although they are very often benign histologically, yet they are practically always incurable.

Our three patients were 43, 56, and 66 years of age, respectively. Their clinical symptoms featured severe pelvic pain with extension to the thigh in two cases. In two cases there

\*Mitotic figures of "normal" configuration are present in the spindle cells of most giant-cell tumors and do not signify malignant neoplasia.

present for four months. This had been "needled" elsewhere. Because no pus had been obtained, the existence of a neoplasm had been suspected, and roentgen therapy had been instituted. There had been considerable loss of weight. The tumor mass, which filled the lower portion of the abdomen as well as the pelvis, was shown by roentgenographic examination to originate from the right ilium. At operation it was found to be irremovable, and biopsy revealed a typical osteogenic sarcoma, grade 2 (on a basis of 1 to 4), with malignant osteoblasts producing an osseomucinous ground substance, the neoplasm being, therefore, truly osteogenic (Fig. 7, c). Death of this patient ensued within a six-month postoperative period in spite of further roentgen therapy.



Fig. 7.—a, Recurrent chondrosarcoma, grade 1. More than one cartilage cell is seen to occupy many lacunae. Mitotic figures are present. A portion of invaded uterine muscle appears at the right (hematoxylin and eosin  $\times 190$ ).

b, Benign pelvic osteochondroma showing the admixture of bone and cartilage. These tumors are not so prone to undergo malignant change as are the purely cartilaginous neoplasms (hematoxylin and eosin  $\times 100$ ).

c, Osteogenic sarcoma of the pelvis, grade 2. Note the formation of calcified and uncalcified osteoid tissue by the malignant groups of osteoblasts (hematoxylin and eosin  $\times 215$ ).

The second patient in the group was most interesting. She gave a two-year history of left hip pain and left sciatic pain. A tender mass was present over the left ilium. Roentgenographic examination showed extensive Paget's disease of the pelvis, spinal column, and skull, complicated by the development of what was interpreted as being a malignant process in the left ilium. It was possible to remove only a portion of this tumor, which microscopically proved to be a fibrosarcoma, grade 3 (on a basis of 1 to 4). The patient died within a six-month postoperative period in spite of roentgen therapy.

It is mistakenly believed that Paget's disease of bone is always a generalized disease. However, roentgenologists have long since shown that the process is much more frequently a localized process and that it is often monostotic.<sup>26</sup> The accepted 5 per cent incidence of "malignant" complications probably is much too high if we include all cases of localized Paget's disease, but it is a complication that we must not forget, for in a review of the literature I have not encountered a single instance wherein bone sarcoma complicating Paget's disease was successfully treated, namely, with the production of a five-year survival. Interestingly enough, fibrosarcoma, rather than true osteogenic sarcoma, is the type of malignant lesion that one usually finds in these cases.

#### IV. *The Miscellaneous Group.*—

Fourteen "tumors," including four metastatic growths, comprised this category, which we so termed because the lesions appeared to arise in or to involve a miscellany of tissues and organs other than those named in Groups I, II, and III.

(a) *Myogenic Tumors* (4 Cases).—In a consideration of myomatous tumors of the intestine Golden and Stout<sup>28</sup> reviewed a number of similar neoplasms of the retroperitoneal region and pointed out the possibility of enteric origin. Pelvic tumors of the type under discussion could arise from the pelvic colon or the rectum, the uterus, or even vestiges of the wolffian apparatus. These same authors emphasized the high incidence of malignant change in retroperitoneal leiomyomatous neoplasms.

All of our patients in this group were adults with narrow age ranges of from 37 to 43 years. In one patient the tumor had been discovered when it was found to obstruct delivery fourteen years prior to admission to the clinic. It had caused her very little trouble in the meantime. Two other patients had signs and symptoms of mild chronic intestinal obstruction for a matter of months. The fourth patient complained of pain and weakness in the left leg of some nine months' duration.

The patient with the fourteen-year history had an encapsulated benign leiomyoma 15 cm. in diameter located behind the rectum and attached to the coccyx. There was no close attachment to the rectum and the tissue of origin remained obscure. Removal was complete and there was no subsequent recurrence over an eight-year period. In the second patient a fibromyoma weighing 2,000 Gm. was intraligamentous on the right and appeared to be of uterine origin. The tumor, which exhibited regions of leiomyosarcomatous change, grade 3 (Fig. 8, c), had produced a left ovarian metastasis having a diameter of 6 cm. and had obstructed the left ureter with the production of hydronephrosis. In spite of pan-hysterectomy and removal of the left kidney along with the tumor there was within eighteen months an extensive recurrence in the right buttock as well as in the pelvis and death occurred twenty-eight months after operation.

The third patient underwent a resection of a retroperitoneal degenerating cystic leiomyosarcoma, grade 1, having a diameter of 12 cm., which apparently had its origin in the mesentery of the small intestine and which had dissected down into the pelvis. A loop of small intestine was intimately attached to a portion of the tumor capsule but in the absence of ulceration of the mucosa it was difficult to implicate this small removed segment as being the source of the neoplasm. The pelvic organs were also included in the extensive removal of tissue. The patient was alive twenty-one years after the operation.

The fourth patient had a specimen removed from a rapidly growing and locally irremovable lesion arising in the region of the left acetabulum. The latter had been partially destroyed and there was an intrapelvic soft-tissue component to the mass. Microscopically this myogenic tumor proved to be a spindle-cell sarcoma, grade 3, showing a scattering of giant cells with finely granular eosinophilic cytoplasm. Although we did not demonstrate bona fide striations, we have tentatively classed the tumor as a rhabdomyosarcoma arising in striated muscle. Roentgen therapy was administered, but the patient died at home four months later.

(b) *Fibroma* (1 Case).—Our twenty-four-year-old patient with fibroma stated that, after a three-month period of chronic sacral pain, her tumor had been discovered during the course of a pelvic examination. Three months later, at examination at the clinic, there were two masses, one nontender, adherent, and presacral, the other tender and adnexal on the right. The adnexal mass proved at operation to be a right tubo-ovarian abscess, which was removed. The presacral mass was found to be ligneous and firmly fixed. Material removed for biopsy proved to be neoplastic rather than inflammatory and to have the microscopic features of a fibroma. There was some resemblance to desmoid tumor. It is interesting to note that this patient, who was living nine years postoperatively, was also able to give birth to a baby "past" her tumor during the follow-up interval.

was difficulty in moving the bowels and in one of these there was a suggestion of rectal sphincteric dysfunction. Each of the three patients had had trouble for one year. One patient gave a history of having undergone partial resection of her tumor and had come to the clinic for consideration of a recurrence. Physical and roentgenographic findings were very similar to those seen in the cases of giant-cell tumor, with notable destruction of the lower sacral segments and the presence of soft-tissue masses. In two instances the lumen of the rectum was compromised but in neither was the mucosa ulcerated. The patient who had undergone resection previously exhibited a small retrorectal draining sinus. Two resections were done at the clinic, both being considered more or less subtotal since the tumors were so extensive. The material submitted to the pathologist was grayish red, friable, and somewhat mucoid, suggesting chondrosarcomatous tissue in some regions and giant-cell tumor in others. The third patient elected to have her operation performed at home, and the local pathologist sent us slides confirming his diagnosis of chordoma. Follow-up letters disclose that two of the three patients died within one year of the time of operation. The third was living but had a recurrence at the time when this paper was written.

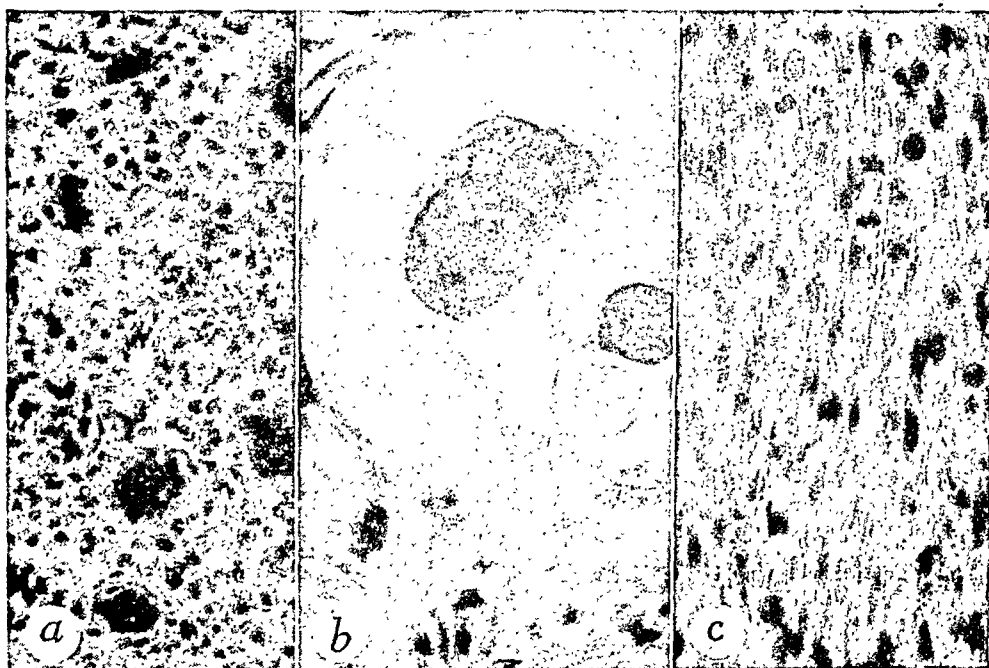


Fig. 8.—*a*, Benign giant-cell tumor of the sacrum. The composition of multinucleated giant cells and the cellular fibroblastic stroma is typical (hematoxylin and eosin  $\times 200$ ).

*b*, Malignant sacral chordoma showing two vacuolated physaliferous cells (hematoxylin and eosin  $\times 340$ ).

*c*, Presacral tumor showing leiomyosarcoma, grade 3. This tumor apparently arose from an intraligamentous "fibroid" and elsewhere showed a benign component. Plump spindle cells with eosinophilic cytoplasm and elongated nuclei with numerous mitoses establish the diagnosis (hematoxylin and eosin  $\times 340$ ).

Microscopically all three tumors exhibited clumps and strands of large, clear, vacuolated polygonal cells in a fibromyxomatous stroma resembling chondromucin. Many giant cells (the so-called physaliferous elements, Fig. 8, *b*) were present. Two of the neoplasms exhibited degrees of cellular anaplasia, normal and abnormal mitoses, and other features consistent with a diagnosis of chordoblastoma (malignant chordoma). The third tumor appeared to be benign. This relatively high incidence of malignancy reflects the small size of our series since in general it is felt that only 20 per cent of chordomas are malignant histologically. Perhaps 40 per cent of malignant chordomas metastasize, but since both of our patients who had malignant lesions were "buried without the benefit of necropsy" we were unable to determine whether or not metastasis had occurred.

type (Fig. 9, a). In this case the metastatic deposits furnished the outstanding features, as they indeed often do. The slow growth of the neoplasm is further evidenced by the fact that the patient did not die until eight years later. We have studied one patient with ileal carcinoid in whom a twenty-five-year period elapsed from the onset of symptoms until death, twenty-one years after resection of the primary growth along with a group of metastatically involved mesenteric nodes.

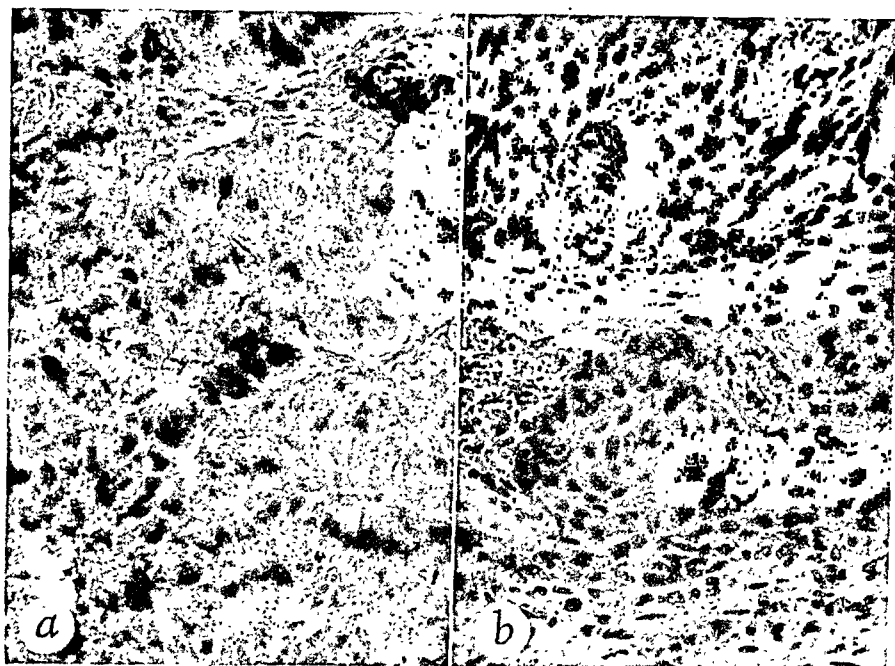


Fig. 9.—*a*, Adenocarcinoma (carcinoid), grade 1, secondary to an undisclosed primary tumor of the gastrointestinal tract. The small prismatic cells are forming pseudo-acini. The patient survived for eight years postoperatively (hematoxylin and eosin  $\times 220$ ).

*b*, Squamous-cell epithelioma, grade 3, secondary to a small growth in the anal canal. Radium and roentgen therapy apparently effected a cure in this patient (hematoxylin and eosin  $\times 200$ ).

A woman, aged 56 years, had her presacral tumor discovered by her local physician whom she had consulted because of a six-week history of backache. Proctoscopic examination at the clinic confirmed the presence of this extrarectal mass and in addition a 2 cm. region of ulceration on the dentate line. Both lesions proved on microscopic examination to be squamous-cell epithelioma, grade 3, the presacral mass being considered as a metastatic deposit (Fig. 9, *b*). Treatment with radium and roentgen rays effected an apparent fourteen-year cure of this patient.

### Symptomatology

It has been stated previously<sup>5</sup> that these presacral or extragenital pelvic tumors are more common among women than among men. In our series it was estimated that these tumors occur about once in every 10,000 admissions of women. It also has been stated<sup>15</sup> that trauma is an exciting factor in producing symptoms. The symptoms vary according to the size and character of the tumor, the origin, the location in the pelvic cavity, the degree of bone erosion and the involvement of the sacral nerves. The most common symptoms encountered in this series were low back pain, sacral pain, unilateral or bilateral leg pain, sciatica, rectal pain, constipation, and generalized abdominal pain. Other symptoms noted were paresthesia, urinary incontinence, vesical pain, indeterminate pelvic pain, indigestion, nausea and vomiting, difficulty

(c) *The Inflammatory "Tumors"* (5 Cases).—There were few "common denominators" in this group of five women with inflammatory presacral swellings. Their ages ranged from 32 to 55 years. One was single, three of the other four had had children and the fourth was pregnant at the time of discovery of the tumor. The smallest tumor was probably on a traumatic basis, since it showed the familiar microscopic picture of fat necrosis. The second patient in the group gave a fourteen-year history of rectal irritation and discharge. A retrorectal abscess was first incised for drainage and later opened widely and packed with gauze, the cavity being allowed to granulate in. A deep posterior anal dimple found by the proctologist was thought to be the source of infection in this case. Relief from operation was complete and permanent.

A third patient stated that a pelvic abscess had been drained and subsequently over a seven-year period repeated incisions and drainages of recurrent right ischiorectal abscesses had been performed. On examination at the clinic a deep anal fistula was conceded to be the source of her trouble. This was excised, and an underlying abscess cavity was treated in a manner similar to that of the second case. Relief was permanent.

Our fourth patient exhibited for one year signs and symptoms of chronic intestinal obstruction resulting from the presence of a ligneous retrorectal mass which was locally tender for the first nine months of its development. There was no evidence of infection about the anus. At the time of colostomy for the relief of obstruction there appeared to be no disease in the pelvic adnexal regions. Biopsy of the mass showed only chronic inflammatory fibrous tissue. One year later it became possible to close the stoma. Three years later, when we communicated with the patient, she was free from symptoms. A Frei test on this patient might have shed some light on our problem.

Our last patient in this group, a woman aged 49 years, had had left sciatic pain for one year. There was a diffuse induration of the retrorectal tissues rather than a well-defined pelvic mass. Biopsy showed only inflamed fat and fibrous tissue containing a few degenerating nerve filaments. One year later this patient died from an uncertain cause and material from an incomplete necropsy was kindly forwarded to us. The retroperitoneal tissues showed only the inflammatory reaction described and this case remains an enigma.

(d) *Metastatic Tumors* (4 Cases).—Our main reasons for including this group in the series is to emphasize that they can occur, that they can overshadow the primary growth as regards size of tumor and production of symptoms, and finally that eradication of them, along with the primary tumor, may occasionally be followed by permanent cure.

A married woman, aged 25 years, stated that she had undergone removal of a left ovarian teratoma weighing 9 pounds (about 4 Kg.). Four months later recurrent pelvic nodules had been removed by the same surgeon. On examination at the clinic two months later there was a retrorectal recurrence which almost obstructed the rectum and vagina. Biopsy material revealed neuroglial tissue, smooth and striated muscle and so forth. All elements appeared benign. This paradox of a seemingly benign neoplasm metastasizing is sometimes seen in complex teratomas, particularly those involving the testis, but it is rarely observed among ovarian tumors of this type.

A married woman, aged 54 years, underwent total hysterectomy and bilateral salpingo-oophorectomy at the clinic in 1914 for ovarian cystadenocarcinoma, grade 1. Seven years later there was a pelvic recurrence which was again treated surgically. One year later her second recurrence took the form of a presacral mass, which compromised the lumen of the rectum. Death occurred in 1922.

After a short history of vague abdominal complaints our third patient, 43 years of age, presented herself for examination. A large fixed presacral mass was found. At laparotomy malignant "implants" were seen to involve the peritoneum and one of these was removed for diagnosis. The pelvic mass was not disturbed, since it was felt to be part of the malignant process, perhaps indeed the primary growth inasmuch as no other primary focus was found. The tissue removed was typical of adenocarcinoma, grade 1, of the carcinoid

those tumors that arise from bone or those that are closely adherent to the bones of the pelvis. Proctoscopic examination is of value in determining that an extrarectal mass is present. As has been mentioned previously, an excretory urogram is almost mandatory in ruling out the presence of an ectopic pelvic kidney. The roentgenologic examination of the pelvic bones and particularly of the anterior sacral wall is of value in those cases in which there is evidence of destruction of bone, and it may be of help in diagnosing an anterior meningocele in those cases in which spina bifida occulta of the sacral vertebrae is present. In this study the roentgenologist reported the presence of a soft-tissue tumor in six instances, evidence of bone changes in twenty-two, and both bone changes and the presence of a soft-tissue tumor in six instances. The results of roentgenologic examination of the pelvis or sacrum were negative in twenty-three cases. Figs. 10, 11, and 12 show the points of interest of the roentgenographic studies. Only by abdominal exploration or exploration through a Kraske incision can one determine the exact nature of these tumors, and of course the final diagnosis rests with the pathologist.



Fig. 12.—Chordoma with expansion of the sacrum which presented anteriorly.

### Treatment

The treatment is surgical removal. In sixty-one cases of this series, the tumor was explored. In one case there was no specimen because the tumor was found to be an anterior meningocele and the meningocele sac was not removed. One patient underwent operation by her local physician, and we were able to obtain slides of the tissue removed for review. In sixteen of the remaining 59 cases, biopsy of the tumor only was performed. In ten cases the tumor was partially removed and in thirty-three the tumor was thought to have been removed in its entirety. In ten cases of the total group, the tumors were thought to be inoperable, and were treated with roentgen rays, radium, or both. Roentgen and radium therapy were used in conjunction with surgical treatment in all cases of malignant lesions. The incision found to give the best approach to these tumors was the posterior or Kraske incision, either with or without removal of the coccyx. Since the majority of these tumors are benign and since the malignant tumors are slow growing with late recurrences and spread by direct extension rather than by blood or lymph stream

in voiding, difficulty in walking, atrophy of the leg muscles, dysmenorrhea, and abdominal distention. A few patients noticed the presence of the tumor before the onset of symptoms. A still smaller percentage of tumors were found during the course of a routine examination.



Fig. 10.—*a*, Ectopic pelvic kidney.  
*b*, Spina bifida of the lower part of the sacrum with anterior meningocele.



Fig. 11.—*a*, Osteochondroma projecting into the pelvic cavity.  
*b*, Chondrosarcoma of the left innominate bone projecting into the pelvic cavity.

### Diagnosis

From the varied symptoms one can see that the symptoms are of little value in the diagnosis. The most accurate means of diagnosis is an adequate pelvic and rectal examination. From the firm fixation one can usually tell



Every available means of diagnosis should be employed to determine the nature of the tumor so that a suitable plan of treatment for pregnant and nonpregnant women may be evolved.

Treatment is surgical removal. Roentgen and radium therapy are important aids in the treatment of these tumors. Since the tumors frequently involve the presacral plexus of veins, hemorrhage offers the greatest obstacle to complete removal. The gynecologist and the general surgeon should know their limitations, since a great many of such tumors involve orthopedic and neurosurgical problems.

Therapeutic abortion is not indicated in those cases in which the patient is pregnant, since the majority of these tumors are benign and since the ones that are malignant recur slowly. If the pregnant uterus has not become incarcerated in the pelvis and the tumor is large enough to obstruct labor, the pregnancy should be allowed to proceed to term, and delivery should be effected by cesarean section. Subsequent removal of the tumor can then be carried out.

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### Discussion

DR. JOHN S. HERRING, New Orleans, La.—In view of the fact that these tumors occurred at the Mayo Clinic only about once in every 10,000 female admissions, it is hardly surprising that most of us see very few of them. I have had none in private practice. I have seen in consultation one case of pelvic kidney obstructing labor, and I recall two cases of pelvic kidney seen personally on the obstetrical service at Charity Hospital in New Orleans, neither of which obstructed delivery, as they were high in the pelvis.

metastasis, we see no indication for therapeutic abortion in those cases in which the patient is pregnant. In some instances it may be necessary to remove the tumor and accept the risk of abortion.

Recently De Voe, Gray, and we<sup>29</sup> reported the surgical removal of a presacral neurofibroma which had produced incarceration of a pregnant uterus (Fig. 9, b). The patient would have aborted had she been left untreated. She recovered from the operation without complication and gave birth to a baby weighing 9 pounds (about 4 Kg.). If the pregnant uterus is well up out of the pelvis, it would seem advisable to let the patient go to term and perform a cesarean section with subsequent exploration of the tumor.

### Summary and Conclusions

Extragenital pelvic tumors of the birth canal were present in a series of 127 female patients presented in this report. Ten patients were considered on the clinical side of the analysis only, inasmuch as they presented presacral tumors which, although not verified pathologically, nevertheless produced a fatal outcome. Symptoms were vague, and findings were not often diagnostic as to type of tumor, the exact nature of which had to be decided by the pathologist. Ten of these tumors were associated with pregnancy.

Pathologically these lesions could be classified into congenital, neurogenic, osseous, and miscellaneous groups. Seventy-two (57 per cent) of the lesions fell into the first category, which featured a high incidence of pelvic ectopic kidneys. One should bear in mind the frequency of this anomaly and confirm the diagnosis by urography rather than at a surgical operation. Teratomas formed another large portion of the congenital group. They were, with one exception, benign. Complete enucleation without spillage was the keynote to successful treatment. Anterior sacral meningocele was a rare lesion, which we felt was best left in capable neurosurgical hands.

Twelve tumors (9 per cent) comprise the neurogenic group. Two subtypes, the ganglioneuromas and neurofibromas, appeared to arise peripherally. Although the various examples were benign histologically, complete surgical removal was not always possible because of fixation. The ependymomas represented unusual extensions of gliomas of the spinal cord and the treatment of these extensive growths was unsatisfactory.

Lesions arising in bone were present in eighteen patients. Purely cartilaginous tumors were generally of a low order of malignancy and most difficult to cure. Tumors exhibiting an admixture of bone and cartilage were slower growing and more responsive to treatment. Two cases of osteogenic sarcoma went on to a rapid fatal termination, one of these representing a complication of Paget's disease. One case of Ewing's tumor was similarly fatal. Giant-cell tumor of the sacrum, although usually benign microscopically, proved malignant clinically in all cases wherein the growth was not small and within the scope of the first resection. The same grim conclusion is even more true of chordomas.

A miscellaneous group of tumefactive lesions contained fourteen examples and included myogenic tumors (often malignant in this location), inflammatory masses (often secondary to anal fistulas), fibromas, and finally, metastatic carcinomas. It is of interest to note that of the seventeen malignant neoplasms found in the entire group of 127 patients, four (24 per cent) were metastatic. Moreover, surprisingly enough, one of the few instances of cure of a malignant tumor in our entire series was that of a metastatic squamous-cell epithelioma, grade 3.

These then are just a few of the more interesting cases that we have had in our series of 127 extragenital pelvic tumors. The gynecologists must be acquainted with the numerous possibilities for points of origin and the pathologist with the peculiar behavior of some of the neoplasms.

DR. JOHN R. WOLFF, Chicago, Ill.—Several years ago I was embarrassed while performing a laparotomy to find that my patient did not have an ovarian cyst, but that the tumor I palpated was an ectopic kidney. Since that occasion I have had the good fortune to observe six patients in whom the diagnosis of an ectopic kidney was established clinically without resorting to surgery. The symptoms of this congenital abnormality are usually vague and not related to this condition, since this kidney is usually a normal organ in an abnormal location. The diagnosis is suggested by the finding of a firm, smooth, non-tender, spheroid, fixed mass deep in the pelvis. It is rather important that one constantly be aware of the possibility of such a mass being an ectopic kidney. In each such instance a retrograde urogram will confirm or rule out this abnormality.

The obstetrical problem presented by a pelvic kidney is one of interest and concern. Many cases of dystocia have been reported, yet in the cases I have seen many had normal vaginal deliveries.

DR. R. B. KENNEDY, Detroit, Mich.—I had two interesting cases sent to me by internists. They each had retroperitoneal pelvic tumors on the right side of pelvis. On removal for biopsy they proved to be Hodgkin's disease.

Another patient, shortly after delivery, developed a large retroperitoneal pelvic mass. The delivery had been spontaneous. This proved to be a lymphosarcoma. I don't believe Dr. Lovelady mentioned Hodgkin's or lymphosarcoma appearing first in the pelvis.

DR. LOVELADY (Closing).—It is gratifying to hear that Dr. Herring's attitude is a conservative one toward the handling of these types of tumors. Not too long ago, Drs. Hunt, Banner, and Dixon from the Mayo Clinic reported several cases of carcinoma of the rectum complicating pregnancy. One was a carcinoid of the colon. It is also interesting that we did not encounter a case of pelvic Hodgkin's disease. Of course some of the inoperable group, of which there were ten, may have been Hodgkin's disease.

In closing I wish to leave two points with you: the importance of the excretory urogram or retrograde pyelogram in ruling out the presence of the ectopic pelvic kidney, and the fact that it is not necessary to produce a therapeutic abortion in these cases where the tumor obstructs the birth canal since the tumors are so slow growing, and those that are malignant tend to recur slowly.

While an ectopic kidney cannot strictly be classed as a tumor, any pelvic mass will offer the same diagnostic and therapeutic problems, and certainly must be considered in a discussion of this type. I remember seeing two cases of carcinoma of the rectum on the Charity Hospital service, one of which was large enough to obstruct labor. From the purely obstetrical standpoint I do not believe that the type or origin of the tumor affects very much the management of the case. If obstruction occurs, the obvious management would be a section. I would be inclined to feel that in any case of pelvic tumor other than one obviously so large or so located as to be absolutely obstructing, a test of labor should be given. We have all seen fibroids which apparently would obstruct labor pushed aside and pulled up to permit normal delivery, and while the mechanism with these is somewhat different, I think such a test would be worth while most of the time.

A thorough and complete examination as outlined by Dr. Lovelady is of course essential for diagnosis. The difficulties presented, are, I think, well illustrated in two cases that I would like to mention.

One is a case which my associate, Dr. King, had while I was in service. The patient's chief complaint was pelvic pain, and scanty menstruation. On routine examination he found a mass in the right adnexa about the size of the fist, rather hard, and felt that it was an ovarian cyst. At laparotomy it proved to be an inflammatory mass involving the cecum, densely adhered to the right adnexa. The final pathological diagnosis was ulcerative lesion of the cecum and terminal ileitis. A resection of the cecum and terminal ileum was carried out. In view of the uncertainties of diagnosis it is always well to be prepared for any necessary procedure.

Another case which I remember is one which occurred at Charity Hospital several years ago. A pelvic tumor had been diagnosed. The surgeon on exploration discovered a retroperitoneal mass and removed it. It proved to be a kidney and the only one the patient had. This, of course, would not occur if the preoperative diagnosis had included a urogram.

DR. N. B. DOCKERTY, Rochester, Minn.—It is manifestly impossible to discuss in a few minutes seventeen different types of pelvic tumors obstructing the birth or any other canal. What I should like to do in this case is to pick one example from each of the four tumor categories given by Dr. Lovelady and say a word about the particular tumor in question.

I have chosen from the congenital group the one which shows an anterior sacral meningocele. In the treatment we must always keep in mind these lesions because they certainly can occur. The treatment of the condition consists in tying off the sac high up where it communicates with the subarachnoid space. You do not have to dissect the meningocele out and run the risk of infection.

From the second or neurogenic group our selection represents the unusual circumstance of a spinal cord glioma extending outside of the central nervous system. Our patient had uterine fibroids clinically and surgically. You can imagine the operator's consternation upon discovering a large ependymoma arising from the sacrum.

In treating these tumors, removal of the presacral portion is the minor part of the operation. There is always extensive tumor within the sacrum, and it extends along the spinal cord and causes paralysis of the lower extremities and of the bladder and rectum.

Our next example is from the bone tumor group, and I have chosen a chordoma because it is not quite as familiar as some of the other types. Like the familiar giant-cell tumor, chordoma is often benign microscopically but, by virtue of extension, paralysis of nerves and infection of bladder and kidney result. Notochordal tissue occurs in all the intervertebral disks but strangely enough 90 per cent of the chordomas arise either in the pituitary region or from the sacrum. They expand and destroy the latter, and, as I said, although microscopically benign, they often kill the patient.

From our miscellaneous group, I have again purposely selected a metastatic cancer. The large presacral secondary component was metastatic from a small growth above the dentate line. This patient was completely cured over a six-year period with radium and x-ray therapy.

instances, however, we are dealing with "pseudoparthenogenesis" which never leads to more than an accumulation of cells within a degenerating follicle. Our definition of "parthenogenesis" stands somewhat between these two extremes. It applies to those processes of cleavage of an unfertilized egg which take place after maturation, in other words after reduction of the number of chromosomes and elimination of polar bodies, regardless how far the development proceeds.

### Literature

Observations of apparent division of unfertilized ova in mammals have been described by numerous authors since Pflueger in 1863<sup>1</sup> gave the first report. An extensive bibliography may be found in Haeggstroem's publication of 1922<sup>2</sup> and Kampmeier of 1929.<sup>3</sup> More recent reports are from Krafka,<sup>4</sup> 1929, Reimann and Miller,<sup>5</sup> 1939, and Baesich and Wyburn,<sup>6</sup> 1945. While in most of these publications the cleavage process of the ovum is described as advancing only to the two, four, six, and eight-cell morula stage, there are a few observations in mammals in which division goes beyond this phase.

In guinea pig ovaries L. Loeb<sup>7</sup> found parthenogenetic development with two distinct formations, placental structures and embryonic structures. He shows pictures of remnants of an embryonal body with tissues which he interprets as ectoderm, endoderm, and mesoderm surrounded by syncytial trophoblast. That a similar fargoing parthenogenetic development may occur also in the male gonad was shown by Peyron,<sup>8</sup> 1940, who describes an embryoma of a human testicle which contains the main elements of early embryonic development: syncytium, amniotoblastic sac, chordomesoblast, chordal canal, embryonic disc, cranial and caudal segments, endoblastic vesicle, etc.

These observations have been very few and their interpretations not completely agreed upon. The fact that even the division of the unfertilized egg into a few cells is a rare occurrence may be seen in the work of Engle,<sup>9</sup> 1927, who studied 100 mouse ovaries and recorded only a single instance of parthenogenesis, one ovum divided into four equal blastomeres.

Why is it that a cell with such an explosive potential of growth like the ovum so seldom grows parthenogenetically without the stimulus of fertilization? What are the conditions under which these exceptions occur? These are the questions we are trying to answer with the help of intravital staining.

### Method and Material

This report is based on the examination of 2,000 microscopic sections from cat ovaries.

It is the same material which was used previously for the study of physiologic development and degeneration of the Graafian follicle.<sup>2</sup>

The cat ovaries were obtained by laparotomy after vital stain had been injected intravenously. Twenty-four ovaries were thus recovered from twelve cats. Ten cats had received a solution of 2 per cent indigo carmine in increasing doses from 50 c.c. to 600 c.c. intravenously, 1 cat 150 c.c. of 0.5 per cent trypan blue, 1 cat 90 c.c. neutral red. The ovaries were cut in serial sections. Every other section was counterstained by different methods. The odd numbered sections received no counterstains and showed the vital stain only.

### Principles

The use of true intravital (not supravital) staining has brought out the fact that the nucleus of a living cell does not take up any such material. It is either stored as granules in the cytoplasm, especially in the cells of organs such as kidneys, liver, salivary glands, which eliminate undesirable substances, or it is primarily deposited in connective tissue spaces between cells all over the body. Finally, it is found in dead and degenerating cells and tissues. If any nucleus

## PARTHENOGENETIC DEVELOPMENT OF THE OVUM AS OBSERVED BY VITAL STAINING\*

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FOR quite a number of years we have been studying the normal histology and physiology of the ovary. It has been our goal to fill certain gaps in our knowledge, especially concerning the development and degeneration of the Graafian follicle.

The first study<sup>1</sup> dealt with the histologic changes which lead to the rupture of the maturing follicle. The theca-interna cone was found as a typical feature of growing human and mammalian follicles. Its tropism toward the ovarian surface indicates that the theca cone has the task of ploughing a pathway through the ovarian stroma to facilitate the ascent of the expanding follicle.

The second study<sup>2</sup> dealt with the physiologic development of the follicle and the degeneration of those which do not reach their destination. Special methods of vital staining by intravenous injection were used to determine the sequence of events leading to either rupture or regression of the normal follicle.

The third study which we present herewith deals with deviations from the normal course of development and degeneration of the Graafian follicle. After having gained a fairly accurate picture of the normal histophysiology, it is not difficult to detect quite a number of abnormalities which do not correspond with the familiar well-established norm. Deviations can occur in all cells and structures of the follicle: the ovum, the granulosa layer, and the theca layers. They are found in all phases of progressing and regressing follicles. Since they are comparatively rare, considerable microscopic material had to be studied before sufficient items had been collected.

The deviations from the norm can be arranged into three distinct groups: the multinuclear ova, the multiovular follicles, and the double follicles.

The first group is the most interesting one. It deals with ova which are going through some form of cleavage without being fertilized. For this reason the generally accepted term "parthenogenesis" is applied. Without going any further we should have a clear understanding of this word. According to Kampmeier,<sup>3</sup> "true parthenogenesis" is the orderly development of a mature unfertilized ovum by regular cleavage into an independent individual or proceeding an appreciable distance toward this goal. In this strict sense parthenogenesis in mammal is extremely rare. The majority of authors, however, apply the term parthenogenesis more loosely "for any real or apparent division of the unfertilized egg cell, irrespective of its maturity and the character, procedure, and order of division" (Kampmeier). This broader definition of parthenogenesis appears practical because it is sometimes difficult to decide whether one is dealing with a mature or immature egg, with an abnormal formation of polar bodies, or some other form of cleavage, mitotic or amitotic. In most of these

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This sequence of events is entirely reversed in follicles which contain ova with some form of division. It must be emphasized at this time that parthenogenesis or pseudoparthenogenesis is found only in degenerating follicles, at least in mammals. This fact has been brought out by several investigators and was especially underlined by Haeggstroem.<sup>5</sup> With this knowledge on hand some light might be thrown on the problem of parthenogenesis by the examination of these ova with vital stain.

### Findings

There are several distinct processes which may be encountered:

#### 1. *Fragmentation of the ovum.*—

Fig. 1 shows such an occurrence. It represents the ovum of a degenerating follicle of a cat. The zona pellucida is deeply stained. It surrounds the cytoplasm which is broken up into several fragments. One of these contains deeply stained nuclear material indicating that this is a dying cell, in which fragmentation is not a result of any form of cleavage.

In this instance the granulosa layer is still alive, the cell nuclei not being stained. The remnants of the egg nucleus, which is split by karyorrhexis, take the stain which is entering the ovum in several places. The fragmentation of the ooplasm is simply part of the general degeneration. Findings like this can be mistaken for parthenogenetic cleavage.

#### 2. *Segmentation of the Ovum.*—

Fig. 2 shows an entirely different picture. The ovum is divided into two equal cells, so-called blastomeres. The nuclei are not visible and therefore have not taken the stain, thus indicating that these cells are still alive. The zona pellucida is stained as we have found to be the case in all living or degenerated ova.<sup>2</sup> The granulosa has undergone the progressive type of degeneration forming a pseudo corpus luteum by growth and fat accumulation. The appearance of small cells migrating through the zona pellucida into the ovum indicates that the degeneration of the ovum is imminent.

This process should be called "pseudoparthenogenesis." There is no sign that maturation of the ovum has taken place. The division of the egg into two equal cells may have occurred before the polar bodies were expelled.

If the ovum is permitted to survive longer inside of a degenerating follicle, the process of division may continue from a two-cell stage to a four- or six-cell stage and beyond.

#### 3. *Parthenogenesis.*—

Fig. 3 represents such an ovum. It is the only one we have found in our material of 24 ovaries. Because of the rarity and significance of this observation illustrations are presented both from the vitally stained and the postmortem stained sections.

This specimen was found in a degenerating follicle. It is characteristic of cat ovaries that when their follicles undergo degeneration the cumulus ovigerus flattens and the ovum sinks to the membrane separating the granulosa layer from the theca interna. At the same time the granulosa commences to grow and to fill the entire follicular cavity. This process is present in our specimen and indicates degeneration of the follicle. The egg is enclosed by a well-preserved zona pellucida. In the hematoxylin-eosin stained section (Fig. 3) we find that small cells have migrated through the zona into the ovum. At the base they are coming from the theca interna in a broad front. At the inner pole they are breaking through small openings from the surrounding granulosa. The main space inside of the zona is not occupied by one individual cell as one would expect. Instead we find six large individual cells, each containing nucleus. The photomicrograph shows only four nuclei, but the drawing (Fig. 4) which combines several sections indicates all six as we found them in serial sections.

takes the stain, it proves the death of this cell. On this basis we could show with the diffuse material we used that in a normally degenerating follicle the ovum, or to be more specific the nucleus of the ovum, is the first to take the stain. From here it progresses as degeneration progresses to the ooplasm, to the inner granulosa layers, to the outer granulosa layers, until finally the entire follicle

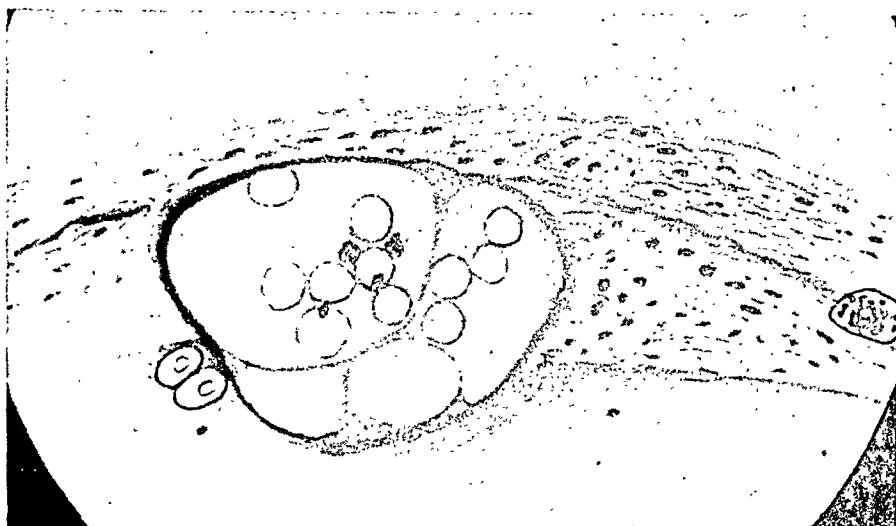


Fig. 1.—Fragmentation of degenerating ovum simulating cleavage. Disintegration not division of ooplasm. Karyorrhexis. Vital Staining.



Fig. 2.—Segmentation of living ovum in degenerating follicle. Egg divided into two blastomeres. Vital Staining.

is stained.<sup>2</sup> In other words vital staining shows that the regular type of follicular degeneration is a process which begins with the death of the egg cell and progresses centrifugally to the outer layers. With vital staining, the beginning degeneration of ovum and follicle can already be diagnosed at a time when no change of cells or structures is histologically apparent. If this process of normal degeneration is arrested it leads to the formation of follicular cysts where the ovum has disintegrated but where the granulosa may persist, until it finally dissolves too.



The division which has taken place in this ovum has to be regarded as true parthenogenesis. In normal maturation there is one large cell which is the ovum and one or two smaller elements which are the polar-bodies. In this specimen there are six cells of more or less equal size. We could not detect any phase of mitotic division. This is an ovum which without being fertilized underwent a development into a six-celled morula. This follicle was found in the ovary of a cat which had received the maximum of intravital stain (600 c.c. of indigo carmine). Under vital stain (Fig. 5) we find the zona pellucida well stained in the portion adjacent to the granulosa. At the base, where the migrating cells enter the ovum it has almost disappeared. From here the stain has flooded the ooplasm but the chromatin in the nuclei remains invisible. It has not taken the stain. We have seen above that this is a sign of life. In other words we are dealing with a degenerating follicle containing an ovum, which is still alive and which is in the process of cleavage, having divided into 6 individual living cells among the surrounding area of disintegration.

There is an essential connection between these two facts which form the basis for parthenogenetic development of the ovum. If the degeneration of the follicle begins in the outer layers (instead of inside the ovum) it stimulates the ovum to cleavage and division. The physical and chemical changes which take place inside of a degenerating follicle seem to provide the impulse which in a still living ovum releases the powers of cell division which otherwise remain dormant until fertilization. That there is some foundation to this conception of parthenogenesis, can be deduced from the famous experiments of J. Loeb<sup>12</sup> who by changing the salt content of ocean water brought eggs of sea urchins into parthenogenetic development of advanced stages.

Our last photomicrograph (Fig. 6) shows parthenogenetic cleavage of the ovum similar to the one seen before but with the important difference that here all elements inside the egg shell are degenerating. There have been at least six individual cells inside the zona pellucida. Six nuclei are visible but they have all the signs of disintegration mostly by pyknosis. The cytoplasm contains vacuoles. The zona pellucida is shrinking from the surrounding follicular layers. This picture shows typically the fate of most of the parthenogenetically divided ova in mammals.

### Discussion

What is the clinical significance of these findings?

There is a group of ovarian tumors which contain derivatives of all three germ layers. Neoplasms of mature character with structures originating mostly from the ectoderm are the dermoids. Neoplasms of unripe character are the so-called teratomas or embryomas. The etiology of these tumors has never been completely solved.

An excellent discussion of the theories proposed to explain the origin of teratoids may be found in the *Encyclopedia of Endocrinology* (Hans Selye, 1946).<sup>13</sup> Only three theories are seriously considered by contemporary pathologists: the parthenogenetic theory, the blastomere theory, and the embryonic theory.

According to the parthenogenetic theory teratoids develop from unfertilized ova, either immature oogonia, or mature ova. Experiments by Bosacus<sup>14</sup> on frogs and toads point strongly in this direction, since he was able to initiate cleavage of unfertilized ova by chemical or mechanical means. Abnormal teratoma-like embryos developed from such ova in the celomic cavity of a host animal.

According to the blastomere theory teratoids originate from fertilized polar bodies or blastomeres separated from the rest of the fetal body. The greatest objection to this theory is that it does not explain that most of these tumors



Fig. 3.—Parthenogenetic development of ovum into six-cell morula inside zona pellucida. Photomicrograph. Hematoxylin-eosin.

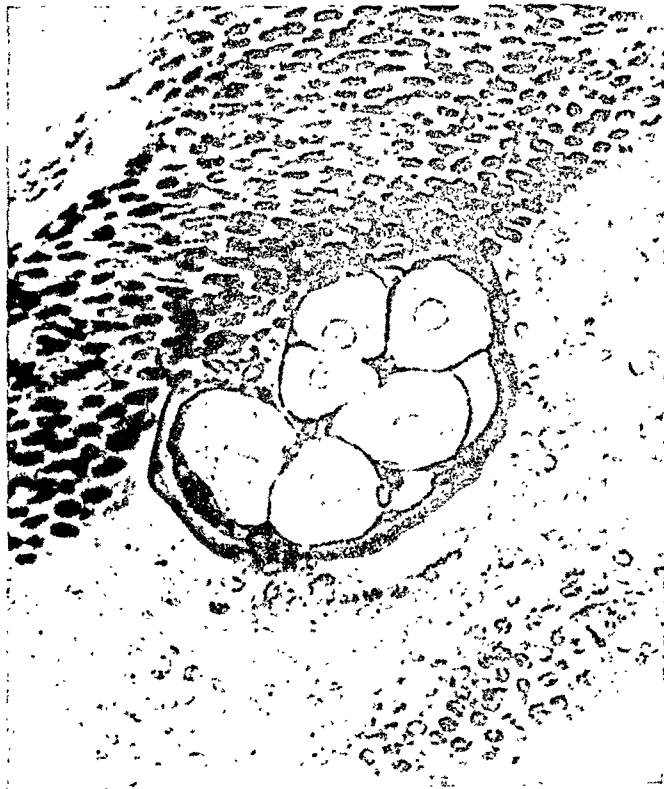


Fig. 4.—Parthenogenetic development of ovum into six-cell morula. Drawing. Hematoxylin-eosin. Note small cell immigration through zona pellucida.

As a matter of fact we could not find any microscopic observation which could be used to prove the blastomere or embryonic theory. There are on the other hand numerous observations which show parthenogenetic cleavage of the ovum with various degrees of development. Our own findings underline the theory that the division of unfertilized ova may lead to the formation of tumors. It is only a question whether these cell clusters degenerate and disappear or whether they continue to live and grow. In the latter instance they will, at least in mammals, never lead to parthenogenetic creation of a whole new individual, but rather to the parthenogenetic creation of tumors showing derivatives of all three germinal layers. There is not structure or cell in the gonads which could produce these tumors other than the germ cells proper. The amazing fact is not that they occur, but that they do not occur more often.

### Summary

1. This paper is based upon observations on vitally stained cats. Stains of various types and concentrations were transfused intravenously into twelve cats. The ovaries were removed under anesthesia and studied in over 2,000 serial sections.

2. In this material a number of deviations from the norm were found. The most important observation concerns forms of cleavage of the unfertilized ovum: fragmentation, segmentation, pseudoparthenogenesis and parthenogenesis. Vital staining gives a clue to the origin of these processes:

3. Physiologic degeneration of the Graafian follicle begins in the nucleus of the ovum and proceeds centrifugally to the periphery. Pathologic degeneration of the follicle begins in the outer layers and proceeds centripetally toward the ovum. If this process is arrested halfway, it leads to typical histologic formations. In the frequent cases of normal regression, follicular cysts are formed. In the rare instances of abnormal regression, it may lead to parthenogenetic development of the ovum.

4. Photomicrographs and drawings of the cleavage of unfertilized ova in various phases are shown. Their significance is discussed in regard to the origin of certain ovarian tumors (dermoid cysts, teratomas, embryomas).

I want to thank Dr. G. G. Robertson, Associate Professor of Anatomy, Baylor University College of Medicine, for checking the embryologic terms used in this paper.

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occur in the gonads and not just anywhere in the body. In addition it is hard to understand that these tumors originate in the female tract of one generation, stay dormant for many years and appear in the gonads of the next generation.

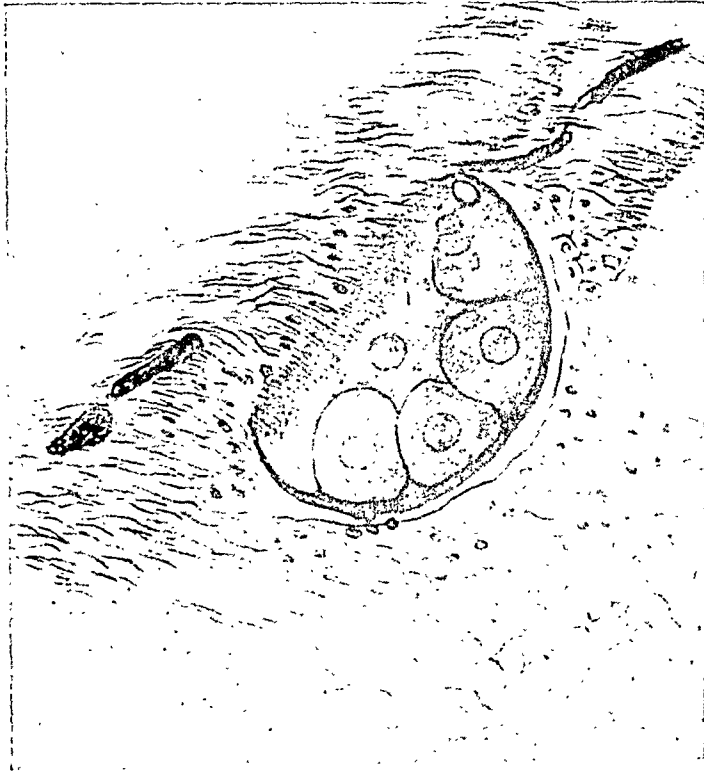


Fig. 5.—Parthenogenetic development of six-cell morula. Unstained chromatin in nuclei indicates egg cells still alive. Vital Staining.



Fig. 6.—Parthenogenetic development of six-cell morula. Shrinkage of zona pellucida, disintegration of ooplasm and nuclei indicate degeneration. Photomicrograph. Hematoxylin-eosin.

The embryonic theory implies that the formation of secondary embryonic axes in the primitive shield is the cause of teratomas. The strongest objection to this theory is also that it does not explain the fact that these tumors are found mostly in the ovaries and testicles.

## THE USE OF PENTOTHAL SODIUM ANESTHESIA FOR CESAREAN SECTIONS\*

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THE first cesarean section under Pentothal Sodium anesthesia at the Coleman Hospital of the Indiana University Medical Center was performed by the senior author in November, 1943. From then until Jan. 1, 1948, there have been a total of 207 sections done under Pentothal. Because of the relatively few articles published relating to this type of anesthesia for cesarean sections, it was thought worth while to present our experience.

In 1944, Hellman, Shettles, Manahan, and Eastman<sup>1</sup> reported 114 sections under this type of anesthesia. Herrick<sup>2</sup> recently reported a series of 492, while Fino and Eisaman,<sup>3</sup> in a preliminary report, listed 40 patients upon whom cesarean sections were done under a combination of local infiltration anesthesia and intravenous Pentothal as suggested by Hunt and Lundy.<sup>4</sup>

Prior to the first of this series, Pentothal Sodium had been used in our department only for very short anesthetics, being restricted largely to dilatation and curettage. At the present time, however, combined with 50 per cent nitrous oxide and oxygen, it is employed in the majority of pelvic operations, being supplemented with curare when increased relaxation is needed. We have not employed it in vaginal obstetrics to any extent because we have felt that only an experienced anesthetist should be permitted to give it. When the latter was not available for cesarean section, we have used other types of anesthesia.

### Technique

Of greatest importance is the fact that the anesthetic is not started until after the patient is fully prepared for the operation, a catheter has been anchored, the abdomen scrubbed and painted and drapes have been placed prior to the injection of Pentothal. In our personal cases of the elective type, Sodium Amytal, 6 grains, and atropine sulfate,  $\frac{1}{150}$  grain, are given three-quarters of an hour before the operation is to begin. Many of the cases were given only atropine sulfate,  $\frac{1}{150}$  grain, prior to operation. There seems to be no appreciable difference in the condition of the baby whether or not Sodium Amytal is given and we have felt that it does lower the apprehension of the patient.

With everything in readiness for operation, a few cubic centimeters of 2.5 per cent solution of Pentothal Sodium are given intravenously and the patient is asleep in a few seconds. In the early cases, O<sub>2</sub> was administered after the patient was asleep. More recently, a mixture of 50 per cent oxygen and nitrous oxide has been given and this has lowered the dosage of Pentothal necessary.

\*Presented at the Sixteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Denver, Colorado, Sept. 23 to 25, 1948.

## Discussion

DR. WILLARD M. ALLEN, St. Louis, Mo.—The findings recorded in this paper by Dr. Strassmann lend considerable support to the idea that certain types of teratomas may owe their origin to spontaneous segmentation of unfertilized ova. This theory is not new. Actually the parthenogenetic theory regarding teratoids is the simplest of all since there is ample evidence from studies of lower forms of animal life that ova may be induced to divide and proliferate without fertilization. Even in the rabbit spontaneous segmentation of the ovum after suitable stimulation with the formation of a fetus has been reported by Pincus. This being so, it requires very little imagination to suspect spontaneous segmentation of germ cells as a cause for teratoids and certain types of chorionepithelioma.

The observation that the ovum may be caused to undergo segmentation when the normal course of events in the retrogression of the follicle is altered is very important. Ordinarily the ovum, if it fails to go through complete maturation, degenerates and at the same time or very soon thereafter the granulosa likewise retrogresses. The great majority of ova and follicles suffer this fate for only a few of the large number of ova found in the ovaries are ever discharged during the process of ovulation. However, Dr. Strassmann finds that in certain very rare instances segmenting ova are found, but these are found in degenerating follicles. The presumption is, therefore, that when the stimulus for the proliferation of the granulosa is withdrawn before the egg has lost its capacity for segmentation unknown chemical factors arising from the degeneration of the granulosa lead to segmentation of the ova and early embryonic development.

Skeptics will say, of course, that the parthenogenetic theory does not explain the primary appearance of the chorionepithelioma in the cranial cavity or in the mediastinum, and the appearance of teratoids in parts of the body widely separated from the gonads. This is not a completely valid objection, however, because of the probability that the primordial germ cells are originally located in the head end of the embryo and subsequently find their way to the genital ridge (see Willier: *Anat. Rec.* 70: 89, 1937).

DR. STRASSMANN (Closing).—I thank Dr. Allen for his discussion. I would like to put one thought into your minds. You may have noticed that the word "hormone" has not appeared in my paper. Of course, the hormones are the very factors which are responsible for the growth and degeneration of the follicle. I have not mentioned these hormones because, if we are truthful with ourselves, here is the biggest gap in our knowledge. I do not mean the ovarian hormones. Fortunately, the ovarian hormones are well-established units. Since we know their chemistry and make them synthetically and since we have them standardized, we can do with the uterus more or less what we want. As one of the speakers said yesterday, we can make an old lady of 81 years of age menstruate. But with the ovary we can do very little. The gonadotropic hormones are not known chemically. We do not know the formula, and we do not have a satisfactory way to standardize them. If you look at it the right way, you need the gonadotropic hormones for half of your gynecology, for half of your sterility cases, and for half of the cases you treat for menstrual disorders. We all depend on using the anterior pituitary hormones and that is the very one thing we do not have to any satisfaction. This one hormone or hormone group is the most important one because it is the key to the function of the ovary, therefore, of the uterine activities and, therefore, of the entire mature life of any woman.

Since this Society represents the gynecologists and obstetricians of over half of the United States, I hope that the true chemistry of the gonadotropic hormones eventually will be determined. We all have used our present commercial preparations. I discarded all of them because I found they are unsatisfactory and most of the time useless. We have got to have the true anterior pituitary hormones. We have to have them standardized—not by the weight-increase of the ovaries but by the weight of the chemical compounds. That would be a big step forward.

TABLE IV. PENTOTHAL SODIUM FOR SECTION FOLLOWING FAILURE OF TRIAL LABOR, 31 CASES

PREOPERATIVE CONDITION				POSTOPERATIVE CONDITION			
MOTHER		FETUS		MOTHER		BABY	
GOOD	FAIR	GOOD	FETAL DISTRESS	GOOD	FAIR	SPONTANEOUS CRY OR RESPIRATION PROMPTLY ESTABLISHED	SEVERE NARCOSIS
30	1	27	4	30	1	30	1

The lengths of the trials of labor before the start of Pentothal and delivery of the baby varied from 5 to 60 hours. The time interval between the start of Pentothal and delivery of the baby varied from 4 to 26 minutes. One mother's condition was considered as only fair before the section because of the existence of essential hypertension of a moderate degree. She withstood the Pentothal anesthesia and section satisfactorily, the baby's condition being excellent. The baby whose condition was poor after delivery had shown marked evidence of fetal distress before the section. Neonatal death occurred after four hours, the autopsy revealing extensive atelectasis.

*Maternal Mortality.*—There was one maternal death in the 207 cases, giving a mortality rate of 0.5 per cent. This patient was a toxic primigravida, No. XC74081, who had been in the hospital under observation and treatment for seventeen days. She had seemed improved when one morning she suddenly went into coma following a convulsive seizure. As she was eight months pregnant with a totally unprepared cervix and had received glucose for several days, we decided that immediate section offered her the best chance. She was given only 0.55 Gm. Pentothal, the operation lasted thirty-three minutes and the baby cried immediately, being extracted eight minutes after the introduction of Pentothal. However, after arousing and talking to her husband, she lapsed into coma and died six hours post partum. No autopsy was permitted.

TABLE V. MORTALITY FOR SECTION UNDER PENTOTHAL SODIUM (UNCORRECTED)

MATERNAL			FETAL		
NO. CASES	DEATHS	MORTALITY RATE	NO. BABIES*	DEATHS	MORTALITY RATE
207	1	0.5%	208	5	2.4%

\*1 set of twins.

*Morbidity.*—In the series, 45 mothers, or 21 per cent, showed morbidity according to the Standard of the American College of Surgeons.

*Infant Mortality.*—There was one stillbirth. The mother of this baby was admitted in shock with central placenta previa and no fetal heart tones. In addition, there were four neonatal deaths, one occurring 4 hours after birth, one 17 hours, one 23 hours, and one 84 hours. Autopsy revealed atelectasis in two cases, extensive pulmonary hemorrhage of undetermined origin in one. The other case was the picture of atelectasis, but no autopsy was permitted. Brief abstracts of the cases with fetal death follow:

CASE 1.—No. 107969. The mother of this infant was admitted to the Coleman Hospital at term as an emergency ward patient in profound shock following profuse hemorrhage from a central placenta previa. Fetal heart tones were absent on admission. Following intravenous glucose, 1,000 c.c. plasma and 2,000 c.c. of whole blood, the mother's condition was sufficiently improved to permit surgery. A low cervical, longitudinal section was performed, a total of 0.4 Gm. of Pentothal Sodium being administered. The baby was stillborn, having succumbed in utero from anoxia prior to the section. The mother's convalescence was uneventful.

In only one case was the abdomen opened under local anesthesia first and then Pentothal administered. All of the early cases had their anesthetic administered by Dr. Greta Gibson, while those since October, 1947, were given by or under the supervision of Dr. Virgil Stoelting.

### Results

The operations were performed by 16 different operators including residents. Three of the staff did 146 operations. Indications are fairly representative of those found in the average maternity hospital. These are given in Table I, while the types of cesarean sections performed are listed in Table II. The incidence of Pentothal Sodium anesthesia for cesarean sections is shown in Table III. It is our opinion that the ideal case for Pentothal is the elective section. However, we have found it satisfactory in cases having had trial labor. Data for this group are presented in Table IV.

TABLE I. INDICATIONS FOR CESAREAN SECTIONS UNDER PENTOTHAL SODIUM

INDICATIONS	NO. OF CASES
Repeat cesarean section	99
Contracted pelvis with trial labor	31
Contracted pelvis (elective)	29
Placenta previa	13
Abruptio placentae	2
Toxemia (failure of medical therapy)	8
Elderly primiparas	5
Multiple uterine fibroids	6
Abnormal presentation { Brow 1 Face 1 Transverse 5	7
Diabetes	3
Previous extensive vaginal plastic	1
Previous myomectomy	1
Previous erythroblastotic baby	1
Bicornate uterus	1

TABLE II. TYPES OF CESAREAN SECTION PERFORMED UNDER PENTOTHAL SODIUM

TYPES OF SECTION	NO. OF CASES
Low cervical:	175
Longitudinal 93 (1 extraperitoneal)	
Transverse 82	
Classical	27
Cesarean hysterectomy	5
Total	207

TABLE III. INCIDENCE OF PENTOTHAL SODIUM ANESTHESIA FOR CESAREAN SECTION AT THE WM. H. COLEMAN HOSPITAL

YEAR	TOTAL SECTIONS	SECTIONS UNDER PENTOTHAL	PER CENT
1943		2	
1944	104	50	47.6
1945	98	48	48.9
1946	89	54	60.7
1947	86	53	61.6



the drug and extraction of the baby. For instance, the second largest dosage of Pentothal given in this series was 2.09 Gm., the time interval was twenty minutes, and yet the baby cried immediately. In another case, twenty-eight minutes elapsed from introduction of Pentothal to extraction of the baby, dosage was 1.4 Gm., yet the latter cried immediately. The largest dosage was 2.250 Gm., interval twenty-nine minutes, and the baby was easily resuscitated by aspiration and hyperventilation. This is graphically presented in Tables VI and VII.

TABLE VI. TOTAL PENTOTHAL SODIUM ADMINISTERED AND ESTABLISHMENT OF RESPIRATIONS IN NEWBORN

TOTAL PENTOTHAL SODIUM GM.	TOTAL CASES*	ESTABLISHMENT OF RESPIRATIONS IN NEWBORN			
		SPONTANEOUS CRY	RESPIRATIONS PROMPTLY ESTABLISHED	MODERATE NARCOSIS	SEVERE NARCOSIS
Not Recorded	27	8	19	0	0
Less than 0.500	1	1	0	0	0
0.500-1.000	59	20	37	1	1
1.100-1.500	95	28	66	1	0
1.600-2.000	22	8	12	0	2
2.050-2.250	3	1	2	0	0
Total	207	66	136	2	3

\*1 Stillborn not included.

1 Set of Twins included.

TABLE VII. TIME ELAPSED BETWEEN START PENTOTHAL AND EXTRACTION OF BABY AND ESTABLISHMENT OF RESPIRATIONS IN NEWBORN

TIME ELAPSED START PENTO- THAL AND EXTRACTION BABY MINUTES	NUMBER OF CASES*	ESTABLISHMENT OF RESPIRATIONS IN NEWBORN			
		SPONTANEOUS CRY	RESPIRATIONS PROMPTLY ESTABLISHED	MODERATE NARCOSIS	SEVERE NARCOSIS
Not Recorded	6	2	4	0	0
0-5	4	1	2	1	0
6-10	65	28	36	0	1
11-15	65	22	43	0	0
16-20	48	12	33	1	2
21-25	10	0	10	0	0
26-30	6	1	5	0	0
31-35	3	0	3	0	0
Total	207	66	136	2	3

\*1 Stillborn not included.

1 Set of Twins included.

### Advantages

From the standpoint of the mother, Pentothal Sodium is one of the most pleasant of anesthetics. She goes to sleep quickly in twenty or thirty seconds and often in the middle of a sentence as she is speaking. Nausea and vomiting upon awakening are very rare. We could find record of only one patient who had nausea to any degree. Bleeding is less than with gas oxygen-ether or cyclopropane. In our series, there was no significant change in blood pressure. The most enthusiastic patients were those of the repeat sections who previously had had some other type of anesthesia including local infiltration and spinal.

CASE 2.—No. 78456. The mother of this infant was a 26-year-old primigravida at term. A low transverse cervical section was performed because of cervical dystocia, uterine inertia, and irregular and rapid fetal heart tones after thirty hours of labor, the membranes having ruptured spontaneously two days before the onset of labor. Plain rectal ether and Nembutal, 3 grains, were given preoperatively. A total of 0.850 Gm. of Pentothal was administered. The baby, extracted ten minutes after the start of Pentothal, weighed 8 pounds, 7 ounces, and showed evidence of severe asphyxia pallida. In spite of repeated aspiration, hyperventilation, and stimulants, respiration ceased four hours after birth. Autopsy revealed extensive bilateral atelectasis. The mother's postoperative course was complicated by a wound infection.

CASE 3.—No. 89213. This baby was delivered by an elective low longitudinal cervical section at term because of cephalo-pelvic disproportion. The preoperative medication was atropine sulfate,  $\frac{1}{150}$  grain. The baby was extracted seventeen minutes after the start of Pentothal—a total of 1.750 Gm. being given for the entire operation. At birth, the baby weighed 5 pounds, 8 ounces. Respirations were established after some difficulty following tracheal aspiration and hyperventilation. Recurrent episodes of cyanosis developed with irregular, rapid respirations. In spite of repeated aspiration, hyperventilation, Coramine, etc., respirations ceased seventeen hours after birth. Autopsy was not permitted, but the clinical picture was typical of pulmonary atelectasis. The mother's postoperative course was uneventful.

CASE 4.—No. 95655. The baby was delivered by low longitudinal cesarean section at eight months' gestation, the indication being a previous section for cephalopelvic disproportion. The preoperative medication was Nembutal, 3 grains, and atropine sulfate,  $\frac{1}{150}$  grain. The baby, 5 pounds, 3 ounces, was extracted sixteen minutes after the start of Pentothal, a total of 1.600 Gm. of Pentothal being given for the entire operation. Respirations were established with difficulty following tracheal aspiration, hyperventilation, and Coramine. Respirations were shallow and irregular with a persistent sternal retraction, and, in spite of repeated aspiration, hyperventilation, and continuous  $O_2$ , respirations ceased twenty-three hours after birth. Autopsy revealed extensive pulmonary atelectasis. The mother's postoperative course was uneventful.

CASE 5.—No. 96578. The baby was delivered by low transverse cervical section at term, the indication being a previous section for contracted pelvis. The preoperative medication was Sodium Amytal, 6 grains, atropine sulfate,  $\frac{1}{150}$  grain. The baby, 5 pounds,  $4\frac{1}{2}$  ounces, was extracted eight minutes after the start of Pentothal, the total amount of Pentothal not being recorded. Respirations were easily established following aspiration and hyperventilation, the baby crying lustily. The baby's condition appeared satisfactory until twenty-four hours after birth, when there was considerable crying and regurgitation of feedings. Forty-eight hours after birth, the temperature rose and the baby was started on penicillin. X-ray of the chest showed only increased bronchial markings. Respiration gradually became increasingly labored, rapid and shallow, death occurring eighty-four hours after birth. Autopsy revealed "Extensive pulmonary hemorrhage due to undetermined cause." The mother's postoperative course was uneventful.

### Immediate Effect on the Baby

Pentothal Sodium passes through the placenta, and, according to Hellman and Shettles, within ten or twelve minutes, reaches equal concentration in fetal and maternal bloods. These authors state that there is a period of five minutes after starting the anesthesia during which the amount of drug reaching the fetus is very small and throughout the first five to ten minutes is decidedly less, as a rule, than after fifteen or twenty minutes of anesthesia. Clinically, we have seen very little correlation in the condition of the baby immediately following delivery with the total dosage of Pentothal and the time interval between introduction of

TABLE VIII. PENTOTHAL SODIUM FOR SECTION IN TONEMIA—8 CASES

HOSP. NO.	MONTH OF GESTATION	TYPE AND SEVERITY	PREOPERATIVE CONDITION		INTERVAL FROM START OF PENTOTHAL TO EXTRACTION OF BABY MINUTES	DURATION OF OPERATION MINUTES	TOTAL PENTOTHAL Gm.	POSTOPERATIVE CONDITION			
			MOTHER	FETUS				MOTHER	BABY*	Lb.	Oz.
73379	7½	Pre-eclampsia, severe. Failure of three weeks' medical regime	Fair	Good	17	40	0.750	Fair	Narcotized. Delayed resp. A & R	3	4
74081	8	Eclampsia—2 convulsions after conservative treatment in hospital for severe pre-eclampsia	Poor	Good	8	33	0.550	Poor. Death 6 hours after sect.	Spontaneous response. Good	4	5½
73398	9	Chronic cardio-renal-vascular disease, moderate	Fair	Good	13	60 Steril.	1.000 N <sub>2</sub> O & Ether	Fair	Good. A & H	5	11
84655	9	Pre-eclampsia, moderate. Failure of medical regime	Fair	Good	11	45 Steril.	1.425	Fair	Good. Spontaneous response	6	3
82889	8	Chronic cardio-renal-vascular disease, severe. Failure of medical regime	Fair	Good	10	65 Steril.	1.375	Fair	Good. A & H	5	6
99160	8½	Pre-eclampsia, moderate. 41-year-old primipara with previous nephrectomy	Good	Good	10	65	? O <sub>2</sub>	Good	Good. A & H	4	15
108994	9	Pre-eclampsia, severe. Failure of medical regime	Fair	Good	8	50	0.750	Fair	Good. Spontaneous response	6	13½
115708	8½	Pre-eclampsia, moderate. Elderly primipara. Failure of medical regime	Good	Good	10	50	0.600 N <sub>2</sub> O-O <sub>2</sub>	Good	Good. A & H	5	3

\*A &amp; H—Respirations promptly established following aspiration and hyperventilation.

## Dangers and Contraindications

Montgomery<sup>5</sup> has pointed out the three groups of cases where Pentothal might be dangerous in obstetrics, namely, toxemia, hemorrhage, and prematurity.

*Toxemia.*—The drug is detoxicated in the liver and the waste products eliminated by the kidneys. In case of extensive damage of the liver, detoxication may not take place. Our one maternal death occurred in this group, while Eastman and Hellman reported one death in their section group. We believe that, in the severe toxemias, particularly when there is a possibility of extensive liver damage, Pentothal should not be used. The same applies to any general anesthesia.

*Hemorrhage.*—Burstein and Hershey<sup>6</sup> pointed out, on the basis of their clinical and experimental observations, the unpredictable effect of Pentothal Sodium on the circulatory system in the face of hemorrhage. In our series were included thirteen cases of placenta previa and two of abruptio placentae (see Table IX). We have seen no untoward effect of the Pentothal, and, in addition, have used it in several ectopics. One case of rupture of the uterus at term, following two previous cesarean sections, was operated upon under Pentothal. However, this patient was not in shock. None of the sections were in shock at the time of operation. We believe that Pentothal should not be given to any patient in shock.

*Prematurity.*—Montgomery<sup>5</sup> states, "Since it is known that pentothal is rapidly conveyed across the placental barrier to the fetal blood stream, and since it has been demonstrated by Dreisbach and Snyder<sup>7</sup> that intravenous pentothal reduces the respiratory activity of the intrauterine animal to a level below one-third, it seems unwise to employ this agent in cases of prematurity for fear of inhibiting the initial respiratory effort in the newborn infant." If there was marked retardation of respiration following Pentothal, certainly it would be manifested in the premature baby. Such was not our experience as evidenced in the data presented in Table X. Here, in one instance of placenta previa, at 7½ months' gestation, the baby weighed 2 pounds, 7 ounces, was easily resuscitated, the mother received 1.2 Gm. of Pentothal, and the time interval was eight minutes. This baby survived. Another baby from a patient with placenta previa weighed 3 pounds, 9½ ounces, and cried immediately, the time interval having been thirteen minutes and the total dose of Pentothal 1.4 Gm.

## Conclusion

Our results of 207 cesarean sections performed under intravenous Pentothal anesthesia are reported. It has been our experience that it is a safe type of anesthesia for both mother and baby in a goodly number of cases when administered by a trained anesthetist. We feel that it is definitely contraindicated in the presence of severe toxemia and in shock from hemorrhage. The ideal place for Pentothal is in the elective section with the mother and baby in good condition. In our experience clinically, time interval between introduction of the drug and extraction of the baby and the total amount of Pentothal administered within reasonable limits show little correlation with the immediate condition of the baby. Pentothal Sodium deserves a place in our armamentarium of obstetric anesthesia for cesarean sections.

TABLE X. PREMATURE BABIES DELIVERED BY SECTION UNDER PENTOTHAL SODIUM—15 CASES

HOSP. NO.	MONTHS' GESTATION	DIAGNOSIS	PREOPERATIVE CONDITION			INTERVAL FROM START OF PENTOTHAL TO EXTRAC-TION OF BABY MINUTES	DURATION OF OPERATION MINUTES	TOTAL PENTOTHAL ADMINISTRATION GM.	CONDITION OF BABY									
			MOTHER	FETUS	MEDICATION				BIRTH		DAYS AFTER BIRTH	DISCHARGE FROM HOSP.						
									WT. LBS.	OZ.		COND.*	LBS.	WT. OZ.	COND.			
73379	7½	Pre-eclampsia, severe	Fair	Good	Sodium Amytal 6 gr. Atropine sulfate 1/150 gr.	17	40	0.750	3	4	Good A & H	60	5	8	Good			
74081	8	Eclampsia	Poor	Good	Sodium Amytal (intravenous) 7.5 gr.	8	33	0.550	4	5½	Good Spontaneous cry	38	6	14	Good			
81095	8½	Placenta previa complete	Good	Good	Nembutal, 3 gr. Atropine sulfate 1/150 gr.	12	50	1.000	4	15	Good A & H	14	5	9	Good			
83416	9	Transverse lie. Failure of bag Rigid cervix Para iii	Good	Good	Nembutal, 3 gr. Atropine sulfate 1/150 gr.	5	35	1.200	5	1½	Fair A & R	12			Good			
85202	8½	Placenta previa Lateral	Good	Good	Atropine sulfate 1/150 gr.	13	58	1.400	3	9½	Good Spontaneous cry	37	5	5	Good			
82889	8	Chronic cardiovascular disease, moderate	Fair	Good	Sodium Amytal 6 gr.	10	65	1.375	5	6	Good A & H	16	5	12	Good			
86006	9	Repeat section (Previous classical section elsewhere)	Good	Good	Atropine sulfate 1/150 gr.	26 Many adhesions	70	1.550	5	5	Good A & H	20	5	10	Good			

TABLE IX. PENTOTHAL SODIUM FOR SECTION IN PLACENTA PREVIA AND ABRUPTIO PLACENTAE—15 CASES

HOSP. NO.	MONTHS' GESTATION	TYPE PLACENTA PREVIA	PREOPERATIVE CONDITION		INTERVAL FROM START OF PENTOTHAL EXTRACTON OF BABY MINUTES	DURATION OF OPERATION MINUTES	TOTAL PENTOTHAL GM.	POSTOPERATIVE CONDITION		BIRTH WEIGHT	
			MOTHER	FETUS				MOTHER	BABY*	LB.	OZ.
81095	8½	Central previa	Good	Good	12	50	1.000	Good	Good. A & H	4	15
75611	9	Partial previa	Good	Good	15	65	1.750	Good	Good. A & H	6	11
85202	8½	Lateral previa	Good	Good	11	58	1.400	Good	Good. A & H	3	9
81472	8	Central previa	Fair	Good	16	40	1.000	Fair	Good. A & H	4	13
46377	9	Partial previa	Good	Good	16	60	1.350	Good	Good. A & H	5	9
105186	9	Lateral previa	Good	Good	15	66	1.450	Good	Good. Spontaneous cry	8	4
105542	8½	Lateral previa	Fair	Good	15	52	1.100	Good	Good. Spontaneous cry	5	2
105565	9	Central previa	Good	Good	18	56	0.750	Good	Good. A & H	8	2
107969	9	Central previa	Fair Admitted in shock	No fetal heart tones	-	25	0.400	Fair	Stillborn	-	-
69819	9	Lateral previa	Good	Good	8	60	0.800	Good	Good. Spontaneous cry	6	13
82819	7½	Lateral previa	Good	Good	8	58	1.200	Good	Good. A & H	2	7
87737	8	Lateral previa	Good	Good	16	55	1.250	Good	Fair. A & R	6	7
69968	9	Lateral previa	Good	Good	15	46	1.125	Good	Good. Spontaneous cry	7	15
98880	9	Partial abruptio	Good	Good	14	45	1.500	Good	Good. A & H	6	3
87115	9	Partial abruptio	Good	Good	?	?	?	Good	Good. A & H	5	7

\*A & H—Aspirations promptly established following aspiration and hyperventilation.

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## Discussion

DR. ROLAND S. CRON, Milwaukee, Wis.—This paper is a very timely one. Recently large series of cesarean sections done under caudal, Pentothal Sodium, with or without supplementary gas, spinal or saddle block anesthesia, have been reported. All of these methods of anesthesia, with the possible exception of caudal which, incidentally, we have discontinued, when administered by competent and experienced personnel have proved to be relatively safe anesthetics for both mother and baby.

Our experience with Pentothal Sodium anesthesia dates back at least ten years. About 96 per cent of our vaginal operations, plastic and hysterectomies, have been done under Pentothal. For more than five years many cesarean sections have been done with an induction of Pentothal Sodium followed by 30 per cent oxygen and 70 per cent nitrous oxide. We agree with the essayists when they advise that in using this type of anesthesia, one should always avail oneself of the services of an experienced anesthesiologist. In general, unless there is some physiological or pharmaceutical reason, the type of anesthesia to be administered to the patient should be left to the discretion of the anesthetist. The one that he or she prefers is the one to be used.

It was indicated in the paper that patients in labor were administered rectal ether plus 6 grains of Amytal, followed by heavy doses of Pentothal. Since Pentothal, Nembutal, and Amytal are all hypnotics, one might question the advisability of administering 6 grains of Amytal before operation. When indicated, we have injected small doses of Amytal intramuscularly. There was a wide variance in the amount of Pentothal Sodium prescribed. The doses varied from 500 to 2,200 mg. This is proof that the agent must be administered by experienced personnel and cannot become a routine procedure. Our average dose for one hour of anesthesia has been 800 mg. with 30 per cent oxygen and 70 per cent nitrous oxide.

Commenting on the four prenatal deaths, one is struck by the very large dose of Pentothal, 1.7 and 1.6 mg., given at sixteen- and seventeen-minute intervals before the delivery of two of the fetuses. It is also well to note that the autopsied baby, dying of pulmonary hemorrhage, may have experienced an overdistention of the alveoli following resuscitative efforts. It is also noteworthy that these babies weighed over five pounds. What do the essayists mean by aspiration and respiration in contrast with aspiration and hyperventilation?

We agree with the essayists that Pentothal should not be administered to the patient in shock or to one suffering from severe toxemia. Neither should this be the anesthetic for the patient with a hemoglobin of 6 Gm. or less.

In spite of the essayists' findings, we think this is not the ideal anesthetic for the delivery of premature infants. We agree that the ideal place for Pentothal only is elective sections. We do not include in this category repeat sections. The performance of this operation is often complicated from the beginning of the operation to the delivery of the baby.

DR. H. M. KIRSCHBAUM, Detroit, Mich.—The use of the intravenous anesthetics in obstetrics is not new. In 1928 I used Pernocton intravenously. My reason for giving it up was that it did not last long enough. Pernocton would last some four hours. In the

81472	8	Placenta previa, complete	Fair	Good	Nembutal 3 gr. Atropine sul- fate 1/150 gr.	16	40	1,000	4	13	Good A & H	90	11	1	Good
66764	8	Repeat section	Good	Good	Nembutal 3 gr. Atropine sul- fate 1/150 gr.	16	60	1,600	5	3	Poor Lived 23 hrs.	-	-	-	Autopsy. Marked atelectasis
46497	9	Repeat section	Good	Good	Sodium Amy- tal 6 gr. Atropine sul- fate 1/150 gr.	8	40	?	5	4 1/2	Good A & H	-	-	-	Death on rd day. Autopsy— Pulmonary hemorrhage, cause un- determined
99160	8 1/2	Pre-eclampsia, moderate	Good	Good	Atropine sul- fate 1/150 gr.	10	65	?	4	15	Good A & H	13	5	5	Good
105542	8 1/2	Placenta previa Lateral	Fair	Good	Demerol, 100 mg. Atropine sul- fate 1/150 gr.	15	52	1,100 50% N <sub>2</sub> O - O <sub>2</sub>	5	2	Good Spontane- ous cry	20	5	6	Good
74620	8 1/2	Previous section Toxemia	Good	Good	Atropine sul- fate 1/150 gr.	12	60	0,900 50% N <sub>2</sub> O O <sub>2</sub>	4	10	Good A & H	21	6	4	Good
115708	8 1/2	Pre-eclampsia Elderly primipara	Good	Good	Atropine sul- fate 1/150 gr.	10	50	0,600 O <sub>2</sub>	5	3	Good A & H	11	5	4	Good
82819	7 1/2	Placenta previa Lateral	Good	Good	Atropine sul- fate 1/150 gr.	8	58	1,200	2	7	Good A & H	80	6	1	Good

\*A & H—Respirations promptly established following aspiration and hyperventilation.



## STERILITY STUDIES IN PRIVATE PRACTICE\*

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SEVERAL considerations have prompted us to report this relatively small series of cases of infertility. We have frequently been surprised to note, in patients consulting us for sterility, that although these patients have previously been seen by doctor after doctor, often including eminently qualified gynecologists, some significant factor has been entirely overlooked or ignored. Many of them, for instance, have had no metabolism test. This is in spite of the fact that almost all investigators who have written on this subject have stressed that a careful, complete routine be followed.

We also feel that in many series reporting results of investigations of sterility, the diagnosis has been too freely applied. It is obvious that if such a diagnosis is applied to a couple who have been married only for a relatively short period of time, many "good results" from treatment will be obtained which are primarily due to allowing Nature to take its course. A year or two of infertile marriage certainly does not necessarily imply a sterile mating, particularly if separations have been frequent or contraceptives used at intervals. Therefore, for the purpose of this paper we have considered that primary sterility exists when the subject has failed to conceive after having been married for longer than three years, without the use of contraceptives, and with regular and frequent intercourse. Secondary sterility is considered to exist if, following a previous pregnancy, no subsequent pregnancy has resulted in five years under the same conditions.

If these definitions are borne in mind, we believe that our results in the treatment of sterility as reported here are good, and that they can be equaled by anyone with a minimum of equipment if a proper routine is followed.

We believe that our results from the use of Lipiodol hysterosalpingography as a therapeutic as well as a diagnostic agent are significant and offer a field for further study.

Rubin<sup>1</sup> has taught us how to study the functional status of the Fallopian tubes, and the use of opaque materials in x-ray visualization of the uterus and tubes has become a routine procedure. Litzenberg<sup>2</sup> first called our attention to the role of hypothyroidism in the causation of sterility. Huhner<sup>3</sup> developed the study of the action of the semen in the female genital organs, and Moench<sup>4</sup> showed us the importance of the evaluation of the number and morphology of the spermatozoa. Reynolds and Macomber<sup>5</sup> stressed the role of the diet

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1934 era there was a great sweep of the use of Evipan intravenously in obstetrics for cesarean section in England, and I note that they, too, have given up the use of the Evipan. While the experienced operator can get the baby out within ten minutes, the senior residents might have difficulty. Pentothal was the same, and showed similar difficulty, in that, if you did not get the baby out quickly, you would have babies that required resuscitation; particularly was this true if any scopolamine was given during the labor.

For that reason, while some papers have been written recently on Pentothal for delivery and cesarean, I would be against it and would stick to the spinal Novocain, 30 mg. for delivery, and 60 to 75 mg. for the cesarean section.

DR. LEON S. McGOOGAN, Omaha, Neb.—I would like to discuss a variation of the type of anesthesia that has been suggested this morning; that is, the combination of local infiltration supplemented by intravenous Pentothal Sodium.

In the five-year period from July 1, 1943, through June 30, 1948, there were 50 cesarean sections done at the University of Nebraska in the charity service, 21 under combined local infiltration supplemented by Pentothal Sodium. In the five-year period from July 1, 1943, through August 10, 1948, on my private service at Omaha, there were 171 cesarean sections, of which 33 were done under combined local and intravenous Pentothal Sodium anesthesia. Of a total of 221 cesarean sections in a period of a little over five years, 54, or approximately 24 per cent, were done using the combination type of anesthesia.

Our procedure for local infiltration is that which I presented in 1946. The local infiltration is done with one per cent Novocain. If the operation is to be a low classical one, the intravenous Pentothal Sodium is administered as soon as the bladder flap dissection is begun. If the operation is to be classical, the intravenous anesthesia is started as soon as the parietal peritoneum of the abdominal cavity has been opened. The total amount of Pentothal Sodium administered is 0.5 to 1.0 Gm. There have been no maternal deaths in the 54 cases. There have been three deaths as far as the babies are concerned, none of which were related in any way whatsoever to the anesthesia that was used.

The amount of the Pentothal Sodium anesthesia is small. The patient has very little, if any, discomfort during the extraction of the baby such as she has under local anesthesia. The combined use of the anesthesia speeds and facilitates the closure. It does not interfere with the uterine contractions. The patient's recovery is smooth and rapid. There are practically no nausea and very little vomiting, and very little postoperative distention. We have no difficulties with the baby's crying.

DR. GUSTAFSON (Closing).—As far as the type of resuscitation is concerned, many of those babies who cried immediately were aspirated. It has been our experience that a baby may cry immediately and still have a tremendous amount of mucus in his trachea, and in a few minutes, if that baby is not watched, respirations may slow down considerably, so it is practically routine on the service to put a catheter down even though he has cried immediately.

In general, we can say that the babies in this series required no greater efforts of resuscitation than those babies delivered vaginally under other types of anesthesia during the same period of years as covered in the study.

As far as the ideal anesthetic for prematurity is concerned, the ideal is probably local infiltration anesthesia, or, if delivered from below, local block. This is simply the experience we had in those few cases of prematurity that were delivered by section under Pentothal.

In answer to Dr. Kirschbaum, in our series, we used local plus Pentothal in the one case. A good many of these patients are not good subjects for locals, appear to be very apprehensive, and for that reason, the staff as a whole has been rather enthusiastic about the use of Pentothal all the way through the operation.

This is not a personal series at all. As I said, there were 16 operators, and it represents the work of the staff over this period, and it is simply our own experience with Pentothal.

potency, but we feel that if large numbers of live, vigorous, and normal spermatozoa are found in the vagina and the cervix, a sperm count and a detailed study of sperm morphology are not necessary. The examination is made one to two hours after intercourse, following a period of abstinence for two or three days. A speculum is inserted into the vagina, and a drop of semen is transferred to a dry slide with a platinum loop. The cervix is carefully cleansed, and a loopful of cervical secretion is secured and placed on a slide. Cotton applicators and pipettes have not been satisfactory for obtaining these smears. We use a platinum loop. If this examination shows that the husband's semen is not satisfactory, he is referred to a urologist for detailed study. Complete absence of spermatozoa can very rarely be corrected, while deficient spermatogenesis may be treated successfully by local therapy, and hormonal administration.

If no abnormality has been found so far in either of the couple, tubal patency is tested by the Rubin method or by uterosalpingography. We prefer the latter for two reasons: first, in some patients the opaque medium has shown the tubes to be open when the Rubin test did not; and second, pregnancies have followed the use of the oil more frequently than the passage of gas. No matter which test is employed, we use it eight to ten days after the first day of a menstrual period. We feel that this is the proper time (a) because we think that the restoration or the improvement of the patency of the tubes three to five days before ovulation enhances the possibility of pregnancy, (b) because there is no possibility of disturbing an early pregnancy, which could occur if the test were performed during the latter part of the menstrual cycle, and (c) because we believe the danger of infection or embolism to be less at this time.

If the tubes are found to be open, and other conditions such as hypothyroidism, endocervicitis, etc., are not present, or are being treated, if found, we order a "nutritive" vaginal instillation before intercourse. We feel that this has at times been of value. We also advise as to the diet of both, counsel a cessation of the "strenuous life," and advocate patience for the next few months. Repeated oil injections may help, even if the tubes are patulous, and are certainly in order if they are closed. We have been able in some women to establish patency at the second or third attempt. If both tubes are closed and repeated oil injections fail to open them, we do not advise attempts at operative correction, unless the patient is fully cognizant of the risk and expense involved, and the low percentage of success.

In studying our patients as above outlined, we found that, as a working basis, we classified and defined the factors as follows.

1. Sterility in the male: For purpose of this study, the male was considered as absolutely sterile if the Huhner test and the urologist's confirmation showed no sperm or no living sperm, the quantity poor with numerous abnormalities; as relatively sterile if quantity, count, and morphology were markedly subnormal, even though living sperm were present. No case was classed as either absolutely or relatively sterile unless either the urologist so stated, or repeated Huhner tests were entirely negative. We found absolute sterility in 9 men, and impaired fertility in 21.

2. "Irregular ovulation": When either on repeated biopsies or by the temperature chart ovulation did not appear to occur regularly, but occurred only occasionally, i.e., not oftener than every three months (one case).

3. Anovulatory: When repeated biopsies and/or temperature charts indicated absolute lack of ovulation.

in relation to sterility. Others, too numerous to mention, have called attention to the questions of the pH of the vaginal and cervical secretions, the viscosity of the latter secretion, the matter of the role of endocervicitis and of cervical anomalies, and of many other conditions which may be factors in the causation of sterility. Hence we must realize now that only by a thorough, step-by-step study of each sterile marriage, with the full cooperation of both husband and wife, can we expect to obtain results. It is well known that even then we cannot expect to solve every sterile mating, and this should be thoroughly understood by each couple at the beginning of the study. Of course there is an explanation in every instance, but we do not yet know enough about endocrinology, degrees of fertility, etc., to find the explanation in the 10 or 15 per cent of sterile matings in which nothing abnormal can be detected by the employment of all the methods of study now at our command.

It is obvious, therefore, that one must study a sterile marriage in such a manner that all possible factors are evaluated. There is nothing new in the routine that we follow, so we shall outline it as briefly as possible.

At the first visit, the fact that the male is almost as often at fault as the female must be stressed. If the husband's cooperation is not forthcoming, the first visit should also be the last. A careful history is obtained covering past illnesses and operations of both partners, especially stressing the possibility of genitourinary infection. The menstrual record of the wife is of particular importance. Inquiry is made as to the frequency of sexual intercourse and its timing in relation to the ovulation time, also as to the questions of impotence, premature ejaculation, malformations, etc. The matter of the ovulation time is explained, and the wife is instructed as to the keeping of a chart. In the matter of frequency the couple of course can hardly be expected to realize that two or three days are required for the elaboration of fully developed spermatozoa. In one of our couples, the reduction of the frequency of intercourse from ten to fourteen times per week to three was all the treatment needed.

Next a general physical examination of the wife is made, and of the husband also, if possible. This is followed by a study of the genitals. In the wife, this should include the search for a possible local infection of the external organs, urethra, vagina, and cervix. The reactions of the vaginal and cervical secretions (no douche that day) are noted, also the amount and character of the cervical secretions. The length and general characteristics of the cervix are studied, and its canal is investigated with a sound or a probe. The size and position of the uterine body are recorded, also the presence of tumors if any, and the adnexal regions are carefully palpated. In most patients, little or nothing of an abnormal nature is found. A retrodisplacement of the uterine body is not thought to be of great moment as a possible cause of sterility, but should be corrected if possible. The examination of the male should include a search for abnormalities such as testicular atrophy or absence, hypospadias, urethral infection, prostatitis, etc.

All patients should be instructed in the keeping of a basal temperature record. If this suggests anovulatory menstruation, or if definite abnormalities are not found, an endometrial biopsy is in order. This is performed on the first day of menstruation, and may be repeated each month for several periods.

Next in order is the determination of the basal metabolic rate on both husband and wife. We have found in several couples that the correction of hypothyroidism in one or both was all that was needed.

We then obtain an estimate as to the character of the husband's semen by the Huhner test. This, of course, gives us only a general idea as to his

TABLE II

Sterile matings studied	118
Pregnancies resulting	34 or 28.8%
Of these 34:	
Abortions (up to 28th week)	6 or 17.6%
Tubal pregnancies	2 or 5.8%
Live babies delivered at term	26 or 76.6%
Live babies delivered at term, percentage of total studied	26 or 22 %

TABLE III

Number of hysterosalpingographies	65
Number of Rubin tests	17
Total	82
Pregnancies following these tests	28 or 34.1%
Deducting those in which other etiological factors were possibly responsible	69
Pregnancies in this group	28 or 40.5%

TABLE IV. TIME INTERVAL OF PREGNANCIES AFTER TESTS FOR TUBAL PATENCY

A. Hysterosalpingography	
Immediately	1
After 1 period	3
After 2 periods	2
After 3 periods	4
After 4 to 6 periods	3
After more than 6 periods	8
	21
B. Rubin Test	
Immediately	2
Before 6 periods	1
After 6 or more periods	4
	7

TABLE V. ANALYSIS OF SUCCESSES

After treatment for	
A. Male sterility	1 (out of 9)
B. Hypothyroidism (as sole factor)	1 (out of 10)
C. Local lesions	2 (out of 7)
1. Cervical infection treated by cauterization	
2. Cervical plug removed	
D. Combined etiology	2 (out of 10)
E. Success after hysterosalpingography	21 (out of 65)
(But 2 other cases are reported under "Mucous plug" and "Combined etiology")	
F. Success after Rubin test	7 (out of 17)

The following case reports illustrate the rather striking results occasionally obtained in our use of hysterosalpingography.

CASE 1.—Mrs. J. P. First seen Oct. 7, 1942, aged 25 years, married two years, no pregnancies. No significant findings. From 1942 to 1947 she was followed regularly, and a complete sterility study carried out, including a Rubin test in 1944, at which time air apparently passed. On May 1, 1947, a Lipiodol hysterosalpingography was done. Patient had a normal

4. Persistently blocked tubes: Where, after one or more air insufflations or hysterosalpingographies, the tubes were never apparently open. We prefer to have the evidence of at least two air insufflations or two hysterosalpingographies; if air, no passage with pressure up to 170 mm. Hg repeatedly; if Lipiodal, no visualization of the tubes. Eleven women were in this group.

5. Apparently temporarily blocked tubes. The tubes were considered to have been temporarily blocked by some cause which was overcome by either air insufflation or hysterosalpingography if the following conditions existed:

A. If, after one or more air insufflations or Lipiodal injections had indicated a blockage, a subsequent similar procedure indicated that the tubes were patent (2 cases). In such cases, if a pregnancy failed to result they are reported as "unsuccessful insufflation or injection" to distinguish them from the following.

B. Where, after a prolonged period of sterility, a pregnancy resulted within a reasonable time following air insufflation or hysterosalpingography, even though the procedure itself indicated patent tubes; i.e., these are the cases in which we believe a therapeutic result was obtained by these procedures. In this group seven pregnancies followed the Rubin test and twenty-one the oil.

6. Hypothyroidism: Where either one or both partners had basal metabolic rate of -20 or below, with no other apparent etiology, or where both had basal metabolic rate of -15 or below. Ten instances in this group.

7. Combined etiology: When more than one factor existed, neither of which alone was sufficient to account for sterility. Ten cases.

8. Local pelvic lesions (see Table I). Eight cases.

9. Etiology undetermined. Self-explanatory.

10. Miscellaneous. Self-explanatory.

The classification of our cases on the basis of etiology as above outlined is shown in Table I. The percentage of success is set forth in Table II, while the results in each etiological group are shown in Tables III and IV. In Table V the time intervals of pregnancies following tubal patency tests are set forth.

TABLE I. ETIOLOGY

1. In the Male:	
A. Absolute	9
B. Impaired fertility	21
2. Irregular ovulation	1
3. Anovulatory cycle (following radium)	1
4. Persistently blocked tubes:	
A. By hysterosalpingography	9
B. By air insufflation	2
5. Apparently temporarily blocked tubes:	
A. Unsuccessful insufflation or Lipiodol injection (therapeutically) although previously closed tubes apparently became patent	2
B. Apparently successful opening of previously blocked tubes	
(1) By air insufflation	7
(2) By hysterosalpingography	21
6. Hypothyroidism	10
7. Combined etiology	10
8. Etiology undetermined	18
9. Miscellaneous local findings which might account for sterility:	
A. Cervical infection	1
B. Fibroids	1
C. Ovarian cyst and fibroids	1
D. Retroflexion of uterus	3
E. Mucous plug in cervix	1
Total	118

## Discussion

DR. GERALD F. BROWN, Grand Forks, N. D.—At the Grand Forks Clinic we have been following an almost identical routine to that presented. Experience has taught us that a few minutes spent in explaining, step by step, what must be done, and in emphasizing that considerable time may be necessary, usually produces understanding, cooperative, and satisfied patients.

The importance of a careful history and complete physical examination cannot be overemphasized. In this problem of sterility where there are still so many unknowns, we must always be alert to find and try to correct any minor deviations from the normal, no matter how trivial they may appear. Thyroid function must be investigated and any degree of hypothyroidism should be corrected. The cervix most certainly should be carefully examined, and any erosions or endocervicitis treated. We attempt to correct any retrodisplacements, even in cases requiring an anesthetic. The uterus is kept in anterior position with a Smith-Hodge pessary. I am sure that most of us have had the experience that such a procedure has solved some sterility problems for us. In couples, when the man is normal, and the only abnormal finding in the woman is a fixed uterine retroversion, I believe that a laparotomy is indicated. In these cases I have usually found the ovaries and tubes prolapsed into the cul-de-sac. Numerous adhesions and small implants of endometriosis are often present. If possible these are freed and a suspension done. We have had several such cases in which the patients subsequently had children.

I must admit that with my patients I have had little success in using basal temperatures for determining the presence or absence of ovulation. The biggest problem stems from the fact that most of the patients have no idea of the meaning of scientific accuracy. Very few are able to read a thermometer exactly—to say nothing of fractions of a degree. Half the time they forget to take their temperature immediately upon awakening.

Endometrial biopsies give much information regarding ovulation. I have been using a small punch biopsy to obtain these specimens. A Randall suction curette is equally satisfactory. Either instrument is small enough, in most instances, to pass through the cervical canal without causing discomfort, and still a piece of tissue large enough for diagnosis is obtained. I have been using this as an office procedure. Biopsies may be taken several times throughout the menstrual cycle so as better to establish ovulation time.

Both the Rubin test and hysterosalpingography certainly have a definite place in sterility studies. Whichever one chooses to use, I feel, is a matter of individual preference. I find that we have been using hysterosalpingography almost exclusively, because we think that a little more information is obtained and our therapeutic results have been better.

I am particularly in accord with the idea that the man involved must be investigated early in the routine. Only recently I saw a case in consultation that demonstrates the importance of this part of the examination. The husband had not been investigated by the referring physician because, "he was a clean-cut and nice appearing young man." The woman, however, had been thoroughly checked. She had a retroversion, and had been advised that a suspension operation would be necessary to correct her sterility problem. It was at her request that the consultation was obtained. To make a long story short, he had an aspermia due to one undescended testicle and one atrophic testicle due to mumps orchitis.

This couple was advised to start proceedings to adopt their children.

DR. I. F. STEIN, Chicago, Ill.—It is my feeling that duration of marriage as the criterion for sterility is outmoded. We now have numerous scientific tests, such as those to determine time of ovulation, which may replace the criteria formerly accepted. The more difficult cases are those cases of infertility where there are no tangible factors to interfere with reproduction.

Charting basal body temperatures is a simple procedure and if one is patient and is willing to devote the necessary time to instruct the patient properly, the results are very satisfactory.

menstruation on May 17, 1947, and on July 1, 1947, a tentative diagnosis of pregnancy was made. Delivered by Cesarean section for contracted pelvis on February 20, 1948.

CASE 2.—Mrs. T. B., first seen Sept. 11, 1947. Married six years, no pregnancies; diaphragm first year. Had had complete work-up elsewhere, with five or six Rubin tests. Had been told that tubes were apparently blocked, but that no other significant factors existed. On Oct. 1, 1947, a Lipiodol hysterosalpingography was done. Patient had last menstrual period on Oct. 17, 1947. Delivered normally July 26, 1948.

CASE 3.—Mrs. S. S. First seen Dec. 4, 1939, married three years, no pregnancies. From then until December, 1940, a complete sterility work-up was done, including a Rubin test in December, 1939, at which time air passed easily. No significant findings. Dec. 28, 1940, a hysterosalpingography was done. Last menstrual period Feb. 17, 1941, delivered normally Oct. 23, 1941.

CASE 4.—Mrs. R. S. First pregnancy delivered Dec. 15, 1938; she had been married nine months at that time. Seen again in March, 1948. Had suspension (elsewhere), 1942. Had had no pregnancies since first delivery. On March 10, 1948, a hysterosalpingography showed that both tubes were definitely blocked. On April 2, 1948, a repeat hysterosalpingography was done and both tubes were reported definitely patent. This patient has not conceived at the present time.

CASE 5.—Mrs. D. D. First seen in February, 1945. Married three years, no pregnancies. A complete sterility study revealed no significant factors. Last menstrual period April 18, 1945. Hysterosalpingography April 27, 1945. Delivered Cesarean section (toxemia) Dec. 31, 1946.

### Summary

In a study of 118 sterile matings, various etiological factors, single or combined, were discovered. Thirty-four pregnancies followed the various methods of treatment employed (28.8 per cent), of which 26 resulted in live births at term, or 22 per cent of the total number studied and treated.

We wish to call particular attention to the results obtained after Rubin tests or hysterosalpingographies where other factors were ruled out, as we believe this indicates a definite therapeutic effect from these measures. We feel that hysterosalpingography is the more valuable of the two, as in most of those where success is reported, one or more previous Rubins had been done without pregnancy resulting. Some of the failures could be explained on the basis of persistently blocked tubes or aspermia of the male, but for many of the failures no adequate explanation could be given. It is felt that operative attempts to correct tubal or spermatic duct blockage have little chance of success. However, operation for the removal of uterine fibroids or ovarian tumors may relieve associated sterility. Success may be anticipated in many patients with hypothyroidism, cervical lesions, transient tubal blockage, and moderately impaired male fertility.

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charts. We haven't had that difficulty. Most of our patients for some reason know how to read a thermometer or can be instructed very easily. He has mentioned biopsies. We were not doing them routinely at the time that these cases went through our hands.

I don't want to have you go away and think we don't treat these patients when they come in at six months or a year. We do. These receive a routine work-up. But we do not include them in this study as they do not fit our definition of true infertility. One case was cited as having been followed from 1942 to 1945 without having had a hysterosalpingography. As I mentioned, when she first came in she had only been married two years and was a very young woman, and it was at her request that we went slow in our studies on her. As to the case where too frequent coitus went on for three years, we didn't let him go on for three years before we stopped it.

As to the timing of a Hühner test, I intended to bring that out. We do the Hühner test at the time we think ovulation is about to occur. The same thing is true for hysterosalpingography. We time them as nearly as we can figure, two or three days before we expect ovulation to occur, because we think that if we open the tubes at that time our chances of success from a therapeutic standpoint are better.

Dr. Garber has mentioned the occupation of the husband. As we said, we try to get a complete history. We ask him what he does and whether he is nervous or whether he is worried. During the wartime, husbands had difficulty because they were under tremendous mental strain. Someone asked about the contrast media used in hysterosalpingography and I knew that was coming. We did not intend to discuss the various media in this paper. We used Lipiodol. In over a thousand cases we have not had serious ill effects. Most of them have been followed over a period of several years. If they were pregnant we followed them subsequently and have not found anything significant.

I have felt that perhaps Lipiodol has a therapeutic effect. I am perfectly open minded, and in the next few months we may use another medium. As far as the use of air is concerned, about the time we decided that we would quit using air we decided to use hysterosalpingography routinely rather than any modification of the Rubin test so we have not used carbon dioxide in very many cases but agree there that it is probably the preferable gas to use.

Basal metabolic determination in the sterility work-ups has proved of little value. Although we do basal metabolic rates on many patients, both male and female, we have little regard for the actual results inasmuch as the obesity patients, even though some may be hypothyroid, do not show low readings. In spite of this, we do use some thyroid but we are not guided entirely by the basal metabolic rate for dosage.

In regard to the Hühner postcoital test, I think it is important to time it in relation to the ovulatory phase of the cycle. My associate, Dr. Cohen, has shown the differences in survival time of the sperm in cervical mucus at the various phases of the menstrual cycle. Survival time was usually twenty to twenty-two hours in the postmenstrual phase, whereas, at ovulation time, when there is a thin, transparent cervical mucus, survival time was from two to six days. The latter is highly significant of the receptiveness of cervical mucus at ovulation time.

DR. S. T. GARBER, Cincinnati, Ohio.—The most significant fact is that four out of five cases were ruled out by the authors as not fitting into the classification for sterility.

The gynecologist is all too frequently approached by an anxious, eager, and impatient young woman who has very recently become an aunt or pseudo-aunt. If she does not conceive within the first month or two, she immediately considers herself sterile and seeks treatment. This she too often receives from the overzealous physician when all that is required is a careful history, a physical examination, particularly to rule out gross pelvic or other disorders, kindly advice or simple instruction and time. Frequently conception occurs within six months as the essayist has indicated. The importance of a careful history cannot be over-emphasized. Later, investigation of the husband, then the wife, may be indicated. A common sense approach is extremely important. A survey of the 400 cases which were ruled out would be welcomed.

May I ask what medium was employed for the hysterosalpingograms; also, were any ill effects encountered?

DR. H. M. KIRSCHBAUM, Detroit, Mich.—I am a little disturbed about this paper because the author says he seeks to save the patient money, and then he has her come to the office from 1942 to 1945 before he tests the tubes. May I say my approach is a little different. I don't wait three years, in fact, I have patients who come to me before they are married to determine if pregnancy is possible. One patient had had an abortion so we tested her tubes to determine their patency. The author describes the use of air. If you will review the literature besides the cases that were never reported, you will find that there were quite a number of deaths with the use of air. For that reason carbon dioxide must always be used. A point that I follow out in my office is to have a model which shows the ovary section so that I can explain to the patient that there are three fundamental things we must know, to determine whether or not she can become pregnant. The one is whether the sperm move in the vagina, and simply taking a Hühner test is not proof the patient doesn't have sperm. If it is negative we must check the acidity factor. If you find no sperm, you must be sure that the patient does not lose the sperm on the way to the office, and in that case a bottle sperm specimen should be brought in.

The Rubin tests must be confirmed by fluoroscopy.

Several patients reported that examinations showed closed tubes with the Rubin test when there was spasm at the internal os. Lipiodol showed this to be incorrect. Sedimentation tests should be done where there is any history of, or doubt about, pelvic inflammation. Antispasmodics should be used as necessary.

I have the patient come before the period and do the Hühner first, and the biopsy before the period, and the test of the tubes shortly after the menses, so that in a very short time we have those three fundamental things established.

DR. HERRING (Closing).—It is impossible to discuss the whole subject of sterility in fifteen minutes. We simply hoped to make a few points that we thought should be emphasized. Dr. Brown has said that he has difficulty in having his patient keep basal temperature

may be perfectly normal menstrual rhythm or occasionally menometrorrhagia, and then it is noted that the periods have become irregular with gradually lengthening intervals and scantier flow. Often this leads to lapses of several months, and then more or less complete amenorrhea lasting for years. Sterility is often of the same duration. We have had a number of patients in this series with amenorrhea lasting from six months to two years. One of the first cases we observed was that of a woman complaining of an amenorrhea of eight years' duration which had followed a period of six years of menstrual regularity.<sup>1</sup> (She has had two pregnancies and regular menstruation following resection.)

The basal temperature charts of patients we have observed clinically generally fail to reveal the ovulatory pattern. Daily vaginal smears likewise lack the changes in cytology characteristic of ovulation. Endometrial biopsies taken at intervals reveal only endometrial hyperplasia with no evidence of secretory activity. Gynecography depicts large globular ovaries and small uterus. The following data are illustrative of the clinical findings in a patient with bilateral polycystic ovaries.

### Case Report

H. L., aged 22 years, married one year. Menses: onset at 15 years, always irregular, at intervals of from three to seven weeks, five days' duration, moderate in amount, with slight premenstrual pain. Her chief complaints were sterility, irregular menstruation, dyspareunia, with the pain occurring in both lower quadrants.

General physical examination revealed a tall, slim, well-proportioned woman. There was no abnormal hirsutism. Pelvic examination showed a small, erect uterus with both ovaries globular, cystic, and tender. In February, 1947, the patient reported that she was amenorrheic for six weeks, nauseated, and languid. Gynecography was advised to verify the palpatory findings. Pneumoroentgenogram revealed bilateral polycystic ovaries (Fig. 1). A temperature chart (Fig. 2) of the next three cycles showed: (1) 31 days, anovulatory; (2) 52 days, anovulatory; (3) 32 days, apparently ovulatory curve. However, an endometrial biopsy taken within a few hours after the onset of the next menstrual period failed to show a secretory phase. Semen examination of the husband showed 111,000,000 spermatozoa per c.c., with 70 per cent motility at one hour, and only 9 per cent abnormal forms.

A bilateral ovarian wedge resection was performed on Aug. 4, 1947. At laparotomy, both ovaries were found to be symmetrically enlarged, about 300 per cent, and contained multiple small follicle cysts. Microscopic section showed a few corpora albicantia but no recent corpora lutea. There were numerous atretic and primordial follicles. The cortex contained numerous follicle cysts lined by granulosa cells and showed much perifollicular fibrosis.

The patient made an uneventful recovery, had two normal menstrual periods, and promptly conceived. She had a full-term, spontaneous delivery on July 3, 1948, eleven months after bilateral ovarian wedge resection. (Pregnancy usually follows in six months to one year after resection.)

From the history and preliminary examination of patients with polycystic ovaries, it is quite obvious that the reproductive mechanism is disturbed or completely interrupted. It is generally accepted that in the normal girl at puberty, one Graafian follicle develops to maturity under the influence of pituitary stimulation, and then ruptures, thus liberating the first ovum. The

## RESULTS OF BILATERAL OVARIAN WEDGE RESECTION IN 47 CASES OF STERILITY\*

### Twenty-Year End Results: 75 Cases of Bilateral Polycystic Ovaries

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CHICAGO, ILL.

AT FIVE-YEAR intervals in the past two decades, we have reported our observations on patients in whom we diagnosed bilateral polycystic ovaries.<sup>1, 2, 3</sup> We have described a syndrome characteristic of this lesion and adapted a surgical technique which has proved satisfactory. Since our first successful operation in 1929, we have operated upon seventy-five patients for this condition with increasingly encouraging results. In this report, we summarize the results of wedge resection of both ovaries in those patients in the group who complained primarily of sterility.

In the past, the prognosis in sterile matings has rested chiefly upon the results of tubal patency tests and the examination of the semen. Fundamental though these tests may be, it is our opinion that insufficient emphasis has been placed upon the reproductive role of the ovaries. More recently, tests for ovulation, such as endometrial biopsy, basal body temperatures, pregnandiol determinations, and daily vaginal smears have been carried out by some physicians to determine the occurrence and time of ovulation.<sup>8</sup> We believe too little attention has been given to changes in the ovaries themselves, particularly in women who do not conform to the ovulatory pattern.

One of the conditions encountered in patients complaining of sterility and amenorrhea, and one too frequently unrecognized, is bilateral polycystic ovaries. In this condition, ovulation occurs very rarely, at long intervals, or not at all, as shown by repeated endometrial biopsies and vaginal smears, basal temperature charts, and suggested by the history of sterility. The prognosis for fertility in these women grows progressively worse unless suitable positive measures are taken.

The symptoms which prompt the patient to seek advice are, in the order of their frequency: 1, amenorrhea; 2, sterility; 3, hirsutism; 4, pain (rarely); and 5, menometrorrhagia (occasionally). Underdeveloped breasts, acne, and/or obesity are more often discovered by the physician than observed by the patient. Many of these women are psychically depressed.

Bilateral polycystic ovaries are associated with a definite syndrome which we have described previously.<sup>3</sup> In this condition, amenorrhea is usually secondary in character. After puberty, and for a period of a few years, there

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first corpus luteum then develops in the ruptured follicle site. This phenomenon starts a cyclic process of monthly follicle ripening and rupture which extends more or less automatically until menopause, interrupted only by pregnancy. There is some controversy as to whether ovulation actually occurs in early menstrual life. This, however, is of purely academic interest and is not pertinent to the subject under discussion.

With polycystic ovaries, we believe there is a hormonal imbalance in which either the Graafian follicle fails to rupture and becomes a retention cyst or the selective action of follicle-stimulating hormone of the pituitary gland may affect multiple follicles simultaneously instead of a single one. Then there develops a condition in which the ovaries contain many small cortical follicle cysts. The ovaries become symmetrically and simultaneously enlarged from one to four times the normal size, are globular or oval, tense, with a thick, gray, smooth capsule. During the development of the multiple cysts, the germinal epithelium becomes thick and fibrous instead of thinning over the site of the maturing follicle. It lacks the normal surface wrinkling usually produced by the contraction of many corpora albicantia. There is also a fibrosis in the stroma ovarii. The cysts contain a clear, colorless fluid under tension, and are a few millimeters to one centimeter in diameter and contain estrin. Rarely are old or recent corpora lutea observed. The micropathology of these lesions has been described in our second contribution.<sup>2</sup>

### Diagnosis

The diagnosis of bilateral polycystic ovaries rests upon a history, symptoms as described above, and the finding on pelvic examination, gynecography or both, of symmetrically enlarged and globular ovaries. Although this enlargement is definite (6 to 7 cm. in diameter as a rule) it is not always easy to recognize by palpation. This is particularly true in obese and masculinized women. Only about 50 per cent have been recognized by us on pelvic examination. These ovaries are relatively small in comparison to ovarian neoplasms but they may be shown accurately on the x-ray film with the use of pneumoperitoneum. This method of partial gynecography is indispensable for the establishment or corroboration of the diagnosis of bilateral polycystic ovaries. We have employed it in almost all of our patients and have separated the cases of the polycystic ovaries from those in which the ovaries were normal or otherwise affected, thus determining which patients required surgical treatment. A presumptive diagnosis may be made on the basis of the typical syndrome, but until the polycystic ovaries can be identified, treatment must be purely empiric. In the normal adult woman, the ovaries normally appear about one-fourth the size of the uterus; in women with bilateral polycystic ovaries, the large, globular ovaries are often from one-half to as large as the corpus shadow on the x-ray film. The x-ray film after pneumoperitoneum is the one reliable and conclusive diagnostic aid in this condition, without which many of these cases might escape detection.

The diagnosis, therefore, is made by: 1, history of secondary amenorrhea (rarely, primary); 2, the finding of bilaterally enlarged and globular ovaries by (a) palpation, (b) gynecography; 3, masculine type of hirsutism; 4, hypoplasia of uterus and breasts. In married women, a history of sterility is significant.

### Treatment

*Medical.*—In the opinion of the authors, there is no accepted medical treatment for bilateral polycystic ovaries. Many of our patients were treated



Fig. 1.—Case H. L. Bilateral polycystic ovaries. Gynecography (pneumoperitoneum).

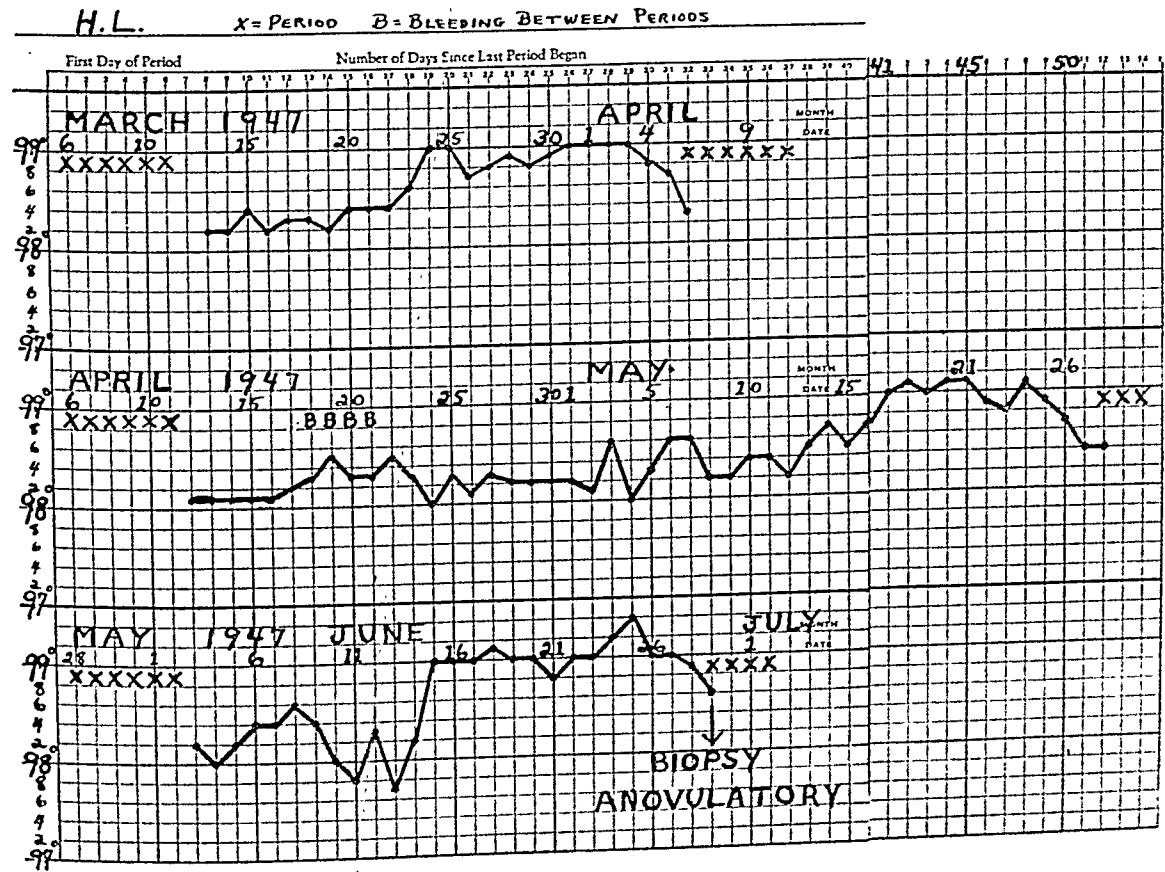


Fig. 2.—Basal temperature chart. Three successive anovulatory cycles.

we required to reoperate for ovarian pain or swelling. In these we found evidence of inflammatory adhesions and in two of the three patients, a single large lutein cyst of the ovary. There was no operative mortality.

### Summary and Conclusions

Although bilateral polycystic ovaries are not one of the common causes of sterility, they are one which is amenable to surgical treatment. Eighty-five per cent of our married patients in whom we diagnosed bilateral polycystic ovaries had a primary complaint of sterility. Therefore, it is evident that sterility is an important component of the polycystic ovary syndrome. Furthermore, 65 per cent of the women who were sterile due to this condition of the ovaries have been successfully treated by bilateral ovarian wedge resection, resulting in pregnancy. Hence, sterility due to this ovarian disturbance has a high rate of curability.

In addition, menstrual function was satisfactorily restored in 89.3 per cent of the seventy-five patients operated upon. We have endeavored to follow these patients carefully ever since 1929 when we did our first resection. The cooperation and response of the patients have been very gratifying. Patients returned for re-examination and sent in menstrual calendars annually to complete our records.

It was noted that the hypoplastic uterus responded to the secondary sex stimulation, as did also the hypoplastic breasts. Hirsutism was not usually favorably affected. In a few patients, however, excess hairy development disappeared to a remarkable degree.

The patients who appeared depressed and frustrated when amenorrheic and presumably sterile showed a remarkable emotional improvement with the establishment of normal menstruation and particularly after pregnancy occurred.

We recommend that the student of sterility become cognizant of the implications of the polycystic ovary syndrome, utilize pneumoperitoneum for corroboration, and perform bilateral ovarian wedge resection to obtain the best results in the treatment of bilateral polycystic ovaries.

We wish to acknowledge gratefully the assistance of Miss Paula Bennett in preparing this report.

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### Discussion

DR. F. L. MCPHAIL, Great Falls, Mont.—This paper demonstrates that surgery is of value in certain cases of sterility. As Dr. Stein points out, this procedure is not a cure-all.

for long periods of time, even years, with endocrine and vitamin products without benefit. Rosenblum and Abarbanel<sup>4</sup> of Los Angeles claim success with large doses of stilbestrol. Their material has not been published so that we cannot evaluate their diagnostic procedures and their conclusions. X-ray therapy to the pituitary and ovary, so enthusiastically recommended by Kaplan,<sup>5</sup> Haman,<sup>6</sup> Mazer,<sup>9</sup> and others, for the purely empiric treatment of amenorrhea, is of questionable value in the treatment of patients with polycystic ovaries. A few of our patients had received x-ray therapy without benefit. None of the supporters of this form of therapy have proved that their series included cases of bilateral polycystic ovaries.

*Surgical.*—When the diagnosis has been established, corroborated by a satisfactory pneumogram, bilateral ovarian wedge resection is our method of choice. A number of techniques have been described in the literature, all of which have the same object in view, namely, decompression of the ovaries to permit ovulation. To this end, various procedures have been described, such as splitting the ovary, decapsulation, multiple punctures, etc., previously reviewed by us.<sup>2</sup> Jacobson's<sup>7</sup> technique is not considered adequate for the pathological condition under discussion. Our method of sharp resection, removing a wedge from each ovary, puncture of the cysts from within, and approximating the edges accurately with fine catgut, has proved most satisfactory in our experience.

*Results.*—Over a twenty-year period, we have performed bilateral ovarian wedge resection upon seventy-five women in whom we diagnosed bilateral polycystic ovaries. The age group, with few exceptions, was 18 to 28 years. Forty-seven were married at the time of surgery; forty (85 per cent) of this group complained primarily of sterility. Of these, twenty-six (65 per cent) conceived one or more times, with a total of forty-six pregnancies. There were thirty-five live births (one set of twins), seven miscarriages, one still-birth, and four not yet at term.

Of the fourteen patients in this group who have not yet conceived, there was a finding of male sterility in five instances. In the other nine, one of the patients died two years after resection from an unrelated condition, and in one instance, the husband died following an automobile accident.

Of the forty-seven married patients upon whom we operated, seven had a primary complaint other than sterility, such as pelvic pain or menometrorrhagia. Following bilateral ovarian wedge resection, five of this group conceived once, one patient giving birth to twins, for a total of six live births.

In addition to the forty-seven patients whom we have discussed above, twenty-eight of the seventy-five were single at the time of operation. About one-half of these were student nurses who complained chiefly of amenorrhea. In all of them the diagnosis was established after transabdominal pneumoperitoneum was performed. Sixteen of the single group subsequently married, eight conceived one or more times, with a total of fifteen pregnancies, eleven live births, three miscarriages, and one not yet at term.

In regard to restoration of menstrual function in the series of seventy-five women operated upon, sixty-seven or 89.3 per cent had regular periods following resection. Menstrual calendars were carefully kept by all of the patients and were returned to us annually. Some of these patients have been followed for twenty years and have shown normal menstrual rhythm interrupted only by their pregnancies. A few of these patients developed fibroid tumors as they approached their "forties." At hysterectomy, we were afforded the opportunity of examining the previously resected ovaries. There was no evidence of recurrence of polycystic formation. In some cases there were omental adhesions to the ovarian scar. In only three patients in the entire series were



Dr. Stein has emphasized the value of wedge resection. We feel that in addition to wedge resection, suspension of the ovary, to insure a normal vascular and lymphatic supply, is of great importance. In a group of experiments conducted by Drs. Weed and Collins in our department at Tulane, it was found that cystic degeneration of the ovary could be produced by prolapse, and a large percentage of these ovaries showed a marked improvement after resuspension and the re-establishment of a normal vascularity. Therefore, in those cases where we do a wedge resection for polycystic ovaries, we also do a careful suspension of the ovaries.

The fact that in a fairly large series of sterility studies we have found only seventeen patients who were suitable candidates for wedge resection and suspension of the ovaries, and the fact that Dr. Stein in over a twenty-year period has selected only seventy-five cases for this procedure should emphasize again that these cases should be selected with great care, and only after due screening, and after adequate trial of more conservative methods. If these precautions are followed, the indiscriminate use of resection of the ovary will not place a very useful and valuable procedure in bad repute.

DR. K. J. KARNAKY, Houston, Texas.—If I understood correctly, Dr. Stein mentioned that Dr. Rosenblum and Dr. Abarbanel had published that some cystic ovaries could be made to undergo atrophy without surgery. Our group at the Jefferson Davis Hospital was first to show that microcystic ovaries can be made to undergo temporary atrophy by the use of 5 mg. of diethylstilbestrol nightly for thirty to sixty nights.\* Stilbestrol is a very excellent drug for causing microcystic ovaries to undergo complete but temporary atrophy. The ovaries at term pregnancy and after stilbestrol in dosage of 5 mg. nightly for thirty to sixty nights appear the same grossly. After stilbestrol is discontinued the ovaries return to normal function and normal menstruation usually ensues. "d e s" stilbestrol has eliminated surgery in many of our microcystic ovaries. The use of stilbestrol in more cases of microcystic ovaries (no ovaries above 5 cm.) may save many women their ovaries and so there will be less gynecological surgery on ovaries. Dr. Stein stated that stilbestrol may produce cystic ovaries. We have not found this to be true. Stilbestrol in large doses causes atrophy of cystic ovaries. We have used this treatment for cystic ovaries for years and find it will save patients from undergoing surgery.

DR. STEIN (Closing).—I trust that the note of conservatism in regard to selection of cases will stick because that was the intention. I think I made it clear that we have made our selections very carefully. Sometimes months have gone by when we did not operate on a case, and we have seen many women with amenorrhea and sterility.

In answer to Dr. McPhail, we do use thyroid. Maybe we use too small doses, ordinarily, about one-half grain a day, unless the basal metabolism rate is low.

In order to differentiate between bilateral polycystic ovaries, a single cyst of the ovary, or a prolapsed ovary which may be cystic, gynecography (pneumoperitoneum) is almost essential for diagnosis, inasmuch as palpation alone is inconclusive. Dr. Weinstein's seventeen cases with eleven pregnancies are extremely gratifying because he got practically the same percentage of pregnancies in his cases that we did.

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\*Karl John Karnaky: A New Treatment for Microcystic Ovaries by the Use of Diethylstilbestrol, *West J. Surg.* 58: 507, 1944.

Careful selection of patients is essential, before resorting to surgery. The history of change from a normal cycle to scanty, irregular periods and finally to a more or less complete amenorrhea is noted, not rarely, in gynecologic practice. This syndrome has been found to precede the positive findings of bilateral polycystic ovaries in some of our patients.

We feel that thyroid therapy is of great benefit in the group of young women presenting the early signs of this syndrome. For that reason we have treated all of our patients presenting signs and symptoms of polycystic ovaries with thyroid for at least six months or longer before resorting to other methods of treatment.

In general, our results with thyroid have been good in the early stages of this syndrome, and poor if the ovarian cysts have become large. We have noted the disappearance of small, bilateral cysts in a number of patients following the use of thyroid. Some of these patients ovulated rarely or not at all, according to the endometrial biopsy, before thyroid therapy was instituted and became pregnant six months to a year after thyroid was taken regularly.

One patient in this series is of interest. At 21 years of age she began a nine-year period of amenorrhea. When first seen, about five years after the amenorrhea developed, she had bilateral ovarian cysts. She was started on thyroid but it was taken irregularly for two years. Then, following two years of continuous thyroid therapy, she began to menstruate irregularly at first and finally on a regular cycle. She had two normal pregnancies with two normal babies following the restoration of a normal cycle.

Dr. Stein has presented one phase of the complex problem of female sterility with an impressive number of cases and with a twenty-year period of observation. He has reported that 65 per cent of forty married women, complaining of sterility, became pregnant following bilateral wedge resection for polycystic ovaries. This is truly a remarkable result.

From the first complete examination of the sterile couple we obtain certain facts. We have one or more sperm counts and examinations. Many times we do not properly evaluate this information. We know that the findings on endometrial biopsies and even on hysterosalpingographic studies are at times misinterpreted. It is, therefore, difficult to evaluate correctly any treatment if there is any doubt in regard to the diagnosis.

It becomes a lifetime problem for one observer to accumulate a large series of patients who have had complete sterility studies and a satisfactory test, first of the various medical treatments and second of any indicated surgery. Of these patients, the most interesting group and at the same time the most baffling is the group of women who ovulate rarely, if at all. Some of these women have bilateral ovarian cysts found at the time of pelvic or gynecographic examination.

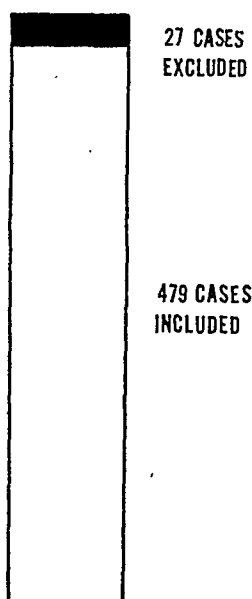
Dr. Stein has offered us a definite plan for treating this group of sterile women, by excision of a portion of each of the bilateral polycystic ovaries. His results are impressive because they are good results and because they represent observations over a long period. The results would be more impressive if the report included a detailed study of each patient including the type of medical treatment, the period of observation prior to surgery, and other pertinent data relating to the sterility problem.

DR. B. BERNARD WEINSTEIN, New Orleans, La.—Dr. Stein's original description (with Leventhal) of the syndrome of polycystic or sclero cystic ovaries associated with anovulation, amenorrhea, mild virilism, and sterility, his utilization of gynecography to clarify the pelvic findings in these cases, and his indefatigable collection of data over a period of some twenty years constitute a signal contribution to one phase of the problem of sterility. Our own results in a limited series of similar cases has been approximately the same.

In 17 women who previously had been carefully studied because of an initial complaint of sterility, and whose husbands had been found to have a normal or high fertility index, and all of whom had previously been maintained on large doses of thyroid—and I should agree with Dr. McPhail on the use and value of thyroid—we obtained a result of eleven pregnancies, or a 64 per cent result, after the patient had been subjected to wedge resection of the ovaries.

7. Did you feel better after the "shots"?
8. If you were to have another baby, would you want the shots?
9. What anesthetic did you have for your last baby?
10. Which anesthesia do you prefer?

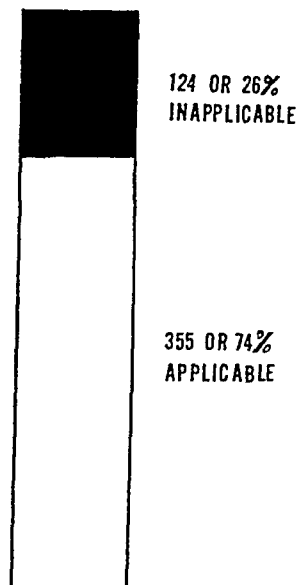
The junior author interviewed most of the patients and an attempt was made to elicit honest and accurate answers to minimize the personal factors involved.



CASES EXCLUDED BECAUSE OF:

ABDOMINAL DELIVERY  
ELECTIVE SPINAL ANESTHESIA  
ELECTIVE INHALATION ANESTHESIA

Fig. 1.



26% OF CASES INAPPLICABLE BECAUSE OF:  
TOO RAPID LABORS  
EXCITEMENT FROM ANALGESIA

Fig. 2.

### Technique of Analgesia and Anesthesia

It was our routine for patients to receive Demerol, 100 mg., and scopolamine, grain 1/130, when labor was definitely established. This was usually defined as a cervical dilatation of approximately 4 cm. in a primigravida, or when uterine contractions were recurring regularly with progressive dilatation of the cervix and descent of the presenting part in a multipara. The Demerol was repeated in one hour if necessary and repeated every four hours as needed. The scopolamine was repeated in a dosage of grain 1/200 each two hours as necessary. When the patient was ready for delivery and after proper preparation of the perineum, the injection of the one-half per cent Novocain was begun. We use the technique described in Beck's *Obstetrical Practice*.<sup>8</sup>

### Analysis of Data

Ideally, it was our purpose to use local anesthesia in all possible vaginal deliveries included in this study. However, we found that we could not use it in 124, or 26 per cent, of the 479 cases. Hence, it was not applicable in one-fourth of our vaginal deliveries. Chief among the reasons was the time element. This was especially true among the multiparas. In some cases, the

## A CRITICAL ANALYSIS OF LOCAL ANESTHESIA AS AN AGENT FOR THE RELIEF OF PAIN IN VAGINAL DELIVERY\*

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LOCAL anesthesia is advocated by many as a satisfactory agent for the relief of pain accompanying vaginal delivery.<sup>1, 2, 3, 4, 5, 6, 7</sup> Its safety, its ease of administration, and the rationale of its use for the benefit of the fetus and the mother are matters of general agreement. However, so far as we know, there is no information available as to how often it can be used for vaginal delivery; and, if used, how successful a procedure it is, as estimated by the patient and the doctor. This study was undertaken for the purpose of answering these questions.

During the period Aug. 1, 1947, to March 1, 1948, pudendal block local anesthesia with one-half per cent Novocain was established as the anesthetic agent to be used for the vaginal delivery of all possible patients on the obstetrical service of the Colorado General Hospital. During this period there were 506 consecutive deliveries. Twenty-seven patients had to be excluded from consideration because of abdominal delivery, elective spinal anesthesia for instruction of the house staff, or an occasional inhalation anesthesia in deference to a patient's wish. This, then, left 479 deliveries which were available for critical analysis as to the general applicability and efficiency of local anesthesia for vaginal delivery. Spontaneous vertex deliveries, outlet forceps, low and midforceps, forceps rotation, and breech deliveries were all included in the 479 patients under consideration. Only version deliveries were considered a definite contraindication for local anesthesia.

### Method of Study

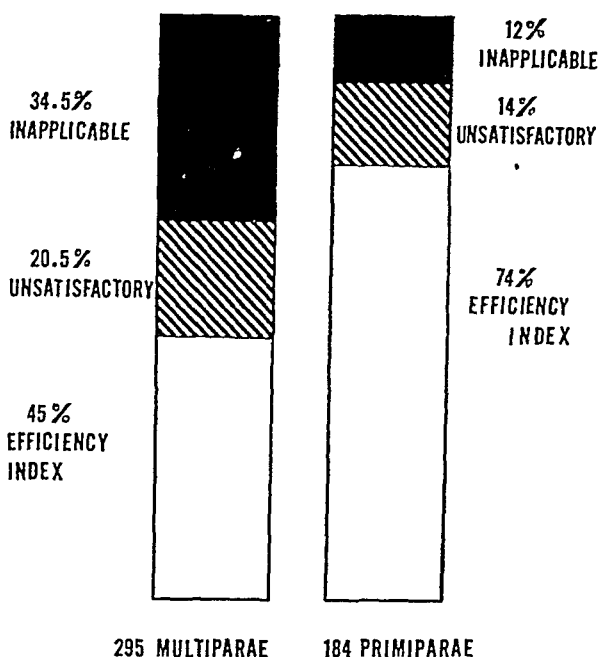
Each of the 479 cases was a potential candidate for delivery under local anesthesia. As will be illustrated in this study, certain elements, inherent in local anesthesia, prohibited its use in some patients.

Within forty-eight hours after delivery, patients were asked a series of questions and their answers plus the reaction of the operator were made the basis of our analysis. These questions were as follows:

1. How do you feel now?
2. Do you remember the baby being born?
3. Did you have much pain in labor?
4. Do you remember going to the delivery room?
5. Did you have pain when the baby was born?
6. Did you have pain in the delivery room?

\*Presented at the Sixteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Denver, Colorado, Sept. 23 to 25, 1948.

iciency index of only 45 per cent. Therefore, we do not believe that local anesthesia is a satisfactory procedure for the delivery of the multiparous patient.



ANALYSIS BY PARITY

Fig. 5.

Of the total 184 primiparous patients, 22 did not receive local anesthesia, and 26 patients from the group that did receive it were dissatisfied. The general efficiency index among the primiparas is thus 74 per cent. Obviously, local anesthesia is better suited to the primiparous delivery than the multiparous. We believe that this is due in part to the difficulty of predicting the course of the multiparous labor and the resultant problem of trying to provide adequate analgesia before delivery. There is no doubt that a labor well sedated enhances the efficiency of local anesthesia.

### Discussion

In addition to analyzing our results, we believe that it will be helpful to set forth certain general recommendations as to the usefulness and limitations of local anesthesia for vaginal delivery.

In the first place, we are certain that local anesthesia is the safest method available to the obstetrician for protection of the mother and child. As a routine for vaginal delivery, it is neither dependable nor efficient as an agent for relieving pain. However, we feel that it should be used when the obstetrician is justified in allowing more than the usual amount of pain for the mother. Such circumstances would be premature delivery, breech delivery, twins, the termination of inertial labor, or maternal disease that contraindicates inhalation anesthesia. In all of these cases, general anesthesia adds a risk to the fetus or mother that might be the difference between a living child or an infant death, minimal bleeding or a postpartum hemorrhage, a living mother or a maternal death. On the other hand, in a normal vaginal delivery, the competent doctor, the well-equipped and well-staffed hospital, the trained anesthetist, the healthy mother and full-term baby are able jointly

inability to get multiparas into the delivery room, prepared, draped, and locally anesthetized in the short period of time afforded by Nature prevented the administration of the anesthetic. In another fraction of these cases, analgesia had excited the patients so much that local anesthesia could not be used.

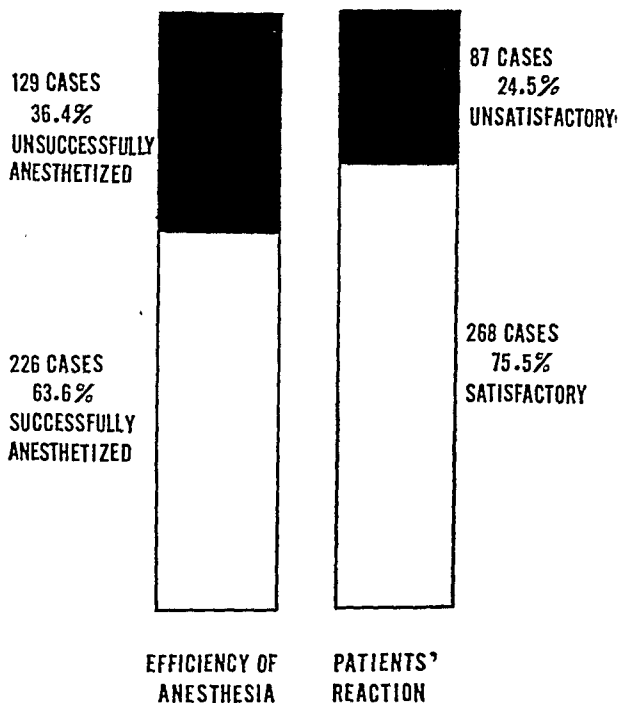


Fig. 3.

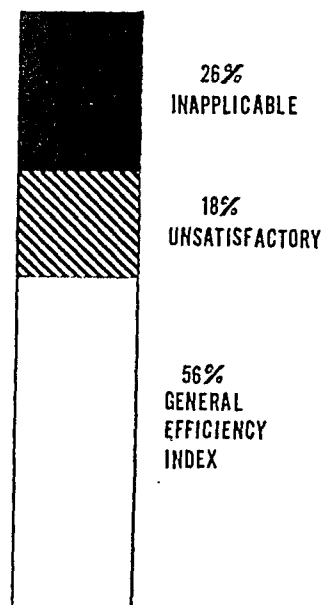


Fig. 4.

Our second objective was to arrive at an efficiency index for local anesthesia for the remaining three-fourths of patients who did receive pudendal block anesthesia. For this part of the study, there were 355 vaginal deliveries. A completely satisfactory result was considered one in which the patient felt no pain for the delivery or the perineal repair. By this standard, 226 (63.6 per cent) of these 355 patients were successfully anesthetized.

Perhaps it is judging local anesthesia too strictly to expect complete relief of pain. With this in view, we questioned the patients as to their appraisal of the anesthesia. Forty-two patients, from the group who felt varying degrees of pain, stated that they were satisfied and, in the case of the multiparas, preferred it to inhalation anesthesia, notwithstanding incomplete loss of pain. With this more liberal standard, then, there were 268 patients, or 74.5 per cent, of those receiving the pudendal block anesthesia satisfied with the procedure.

To arrive at a general efficiency index, it is necessary to eliminate the 124 patients whose labors were too rapid or who were too uncooperative and the 87 patients for whom local was used and found unsatisfactory. Thus, in 479 unselected vaginal deliveries, we were able to use local anesthesia successfully for only 268 patients, or 56 per cent of cases.

It is interesting to analyze the failure group on the basis of parity. Of the total 295 multiparous patients, 102 did not receive local anesthesia for the reasons already indicated, and 61 patients from the group that did receive it were dissatisfied. Hence, among the multiparas, there was a general ef-

6. Primiparous patients were found to have a general efficiency index of 74 per cent as compared with 45 per cent among the multiparous patients and the reasons for this were enumerated.

7. A positive recommendation for the use of local anesthesia in certain types of deliveries is made. These include premature deliveries, breech deliveries, twins, inertial labors, and constitutional diseases in the mother in which general anesthesia is contraindicated.

8. The use of local anesthesia as a routine procedure in the normal delivery is not recommended.

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4200 EAST NINTH AVENUE

### Discussion

DR. CHAS. E. GALLOWAY, Evanston, Ill.—Dr. Taylor and Dr. Jack are to be commended for approaching this matter of local anesthesia with open minds, doing a thorough investigation and then making what might be termed an adverse conclusion. Too many so-called investigators seem to investigate their problems with determination on their part to prove their original contentions.

One of the most dangerous situations we, as obstetricians, find ourselves in is when we are called upon to deliver a patient in fairly rapid labor who has just gotten up from the table with a full stomach. She generally demands anesthesia the same as all the others. Every hospital has had aspiration deaths, pneumonia, or lung abscess from such cases. Here local anesthesia is much safer than any form of general anesthetic. Local anesthesia is also very useful in home deliveries or where trained assistants are scarce. It is also indicated when the patient has a severe upper respiratory infection or pulmonary tuberculosis. I agree that every obstetrician should be proficient in its use. We must, however, always teach that the patient comes to the hospital to deliver the baby and not for the purpose of being anesthetized.

I doubt if cardiac patients should have local anesthesia; ether seems more beneficial to the patient and frees the obstetrician at a time when minutes count. Patients with inertia also many times should be delivered earlier than the perineal stage and local anesthesia many times stops uterine contractions even in normal labors. Premature babies should certainly have local or spinal anesthesia and we should also deny the mother analgesia. No patient having a premature baby should receive Demerol and repeated doses of scopolamine or any of the other drugs commonly used for relief of pain in labor. Also, local anesthesia does not seem indicated in breech delivery if some other anesthetic is available. I cannot agree that breech delivery is a positive indication.

Local anesthesia is time consuming for the obstetrician and is not without risk. One investigator recently reported six cases of ischioirectal abscess following its use. Great care must be used to avoid entering the rectum and the needle must always be kept moving to avoid transfusing the solution into the circulation. When depositing a large amount in one place back pressure must always precede the injection.

In local anesthesia as in everything else, the quality of the solution being used is also very important. Personally, I prefer 1 per cent solutions of Novocain rather than one-half

to assume and balance the risk of a well-conducted general anesthetic. If any one of these essential elements is lacking, the mother or baby must bear the larger risk, and therein lies a very positive indication and recommendation for local anesthesia.

We feel strongly that every obstetrician should be proficient in the use of local anesthesia. We feel that certain patients should never be given the added risk of general anesthesia no matter how expert the team supervising her accouchement. We recommend that all premature infants, breech presentations, and twins be delivered under local anesthesia for the benefit of the fetus. Local anesthesia should be used for the delivery of all primary and secondary inertia cases in order to prevent postpartum hemorrhage in an already atonic uterus. Cardiac patients and those with diabetes or pulmonary disease should be delivered under local anesthesia.

### Summary

Four hundred seventy-nine unselected vaginal deliveries have been studied for the purpose of estimating: first, how often can local anesthesia be used; and second, if it is used, how efficient is local anesthesia as an agent for the relief of pain? Local anesthesia was used in every case of the 479 patients where possible. All of the patients were questioned within a forty-eight-hour period post partum to obtain their estimate of the local anesthesia used. The results of the analysis showed that one-fourth of the patients admitted to the hospital for vaginal delivery were cases for which local anesthesia was not applicable. This one-fourth of patients either delivered too quickly for the operator to give local anesthesia or the patient was too uncooperative due to her previous analgesic medication. Of the cases in which a pudendal block anesthesia was used, 75 per cent were successes and 25 per cent were failures from the viewpoint of the patients when interviewed.

Since local anesthesia is being advocated as a simple and efficient method of pain relief for vaginal delivery, an objective study was undertaken to determine the limitations and general efficiency of local anesthesia in obstetrics.

### Conclusions

1. A study is reported which was undertaken to provide information as to how often local anesthesia can be used in vaginal delivery and, if used, how successful a procedure it is.
2. Twenty-seven cases had to be excluded because of abdominal delivery, spinal anesthesia for instruction of the house staff, or inhalation anesthesia in deference to a patient's desire.
3. Twenty-six per cent of the remaining 479 cases were found to be inapplicable for local anesthesia.
4. Thirty-six and four-tenths per cent of those 355 receiving local anesthesia were found to have had some degree of pain with the delivery or repair but only 24.5 per cent were personally dissatisfied with the procedure.
5. A general efficiency index for 479 unselected vaginal deliveries was found to be 56 per cent.



that there are two schools of thought on breech delivery. We are very well satisfied with using the voluntary efforts of the mother as much as we can; and in giving oxygen to the mother during the expulsion of the fetus; and in assisting the breech where necessary, but coming as close to a spontaneous breech delivery as possible. I realize that is at variance with some other men's practices.

There is one rule that we try to follow on anesthesia, as Dr. Galloway pointed out when he mentioned that the woman, after all, comes to the hospital to have the baby and not to have an anesthesia. This is that, if there is any doubt about what anesthesia a woman should get, she should not receive any anesthesia that will make the risk of that procedure greater than the risk of having a baby. When the risk of having a baby is one to one thousand how can we justify using an anesthetic agent that carries a risk for life greater than that? I endorse what he says about no analgesia or general anesthesia for mothers giving birth to premature infants.

I think that if a postpartum hemorrhage is anticipated, or a breech is to be delivered, or the mother has heart disease, or if the fetus is premature, local anesthesia is especially useful. But I do not think that trying to use it in our hospital as a routine procedure for all cases is going to make us very popular with the patients. As Dr. Stacy said, in training residents and interns who do take too long to repair an episiotomy, local anesthesia is helpful.

per cent and the solution should not be autoclaved because by this procedure it loses some of its potency. We prefer to use 5 c.c. ampules of 20 per cent Novocain with Cobefrin and dilute it with normal saline at the time it is to be used. Made up solutions of Novocain kept as stock in the operating room not only have been autoclaved once, but may have had several such treatments.

There is one other useful place for local anesthesia in vaginal delivery. When the patient has delivered before anesthesia could be given and there is repair work to be done, a much better job can be done if one carefully injects the perineum with Novocain.

DR. A. F. LASH, Chicago, Ill.—I think local anesthesia is as much a part of anesthesiology as bread is of one's diet. I have seen the various other types of anesthesia introduced and dropped, but have found that local anesthesia has remained and has proved most efficient. I certainly find it of great value for women who come in with respiratory infections and toxemias. I certainly disagree with Dr. Galloway about breech deliveries. I think it has removed much of the fear of delivery and of fetal mortality. By retaining the active efforts of the mother and by pudendal block anesthetizing the perineum, it allows an episiotomy to be done so that she has the passage open and delivers the breech as well as she would a cephalic presenting part.

We are beginning to appreciate the importance of anoxemia in the babies. Local anesthesia permits oxygen to be administered, thereby preventing anoxemia of the child's brain and the many complications incident to this anoxemia, such as multiple cerebral hemorrhages, scars, spasticity, and subnormal mental development.

DR. KENNEDY, Detroit, Mich.—Mr. Chairman, I would like to substantiate what Dr. Galloway said for general anesthesia in breeches. Under caudal or spinal in breeches the baby is stimulated to breathe too quickly and often aspirates amniotic fluid or vaginal contents before the head is delivered. I used caudal anesthesia in forty breeches and found it was necessary to aspirate most of the tracheas.

I would also like to make a plea for the use of caudal or continuous spinal or saddle block in premature labor. The mother is comfortable, the labors are shorter, and the premature baby has no depressing effects from analgesics.

DR. J. C. STACY, Tupelo, Miss.—I am in the position of being more or less forced to have the men who work with me do local infiltration and not local anesthesia as such. We have a group of younger men coming into the service, and it is necessary to formulate certain rules and regulations, things they can do and cannot do. For instance, we have to forbid them to use spinals because, in their anxiety for the patient and perhaps trying to give relief, spinals have been given and the patient would not deliver for four or five or six hours. It was a case of misjudgment. Others would do saddle blocks and let the patient precipitate. We have formulated a rule that the patients be given Demerol perhaps to take off the edge. There is no attempt to produce amnesia. We are forbidden and do not allow them to use hyoscine in any form. Perhaps we are a little scared of edema of the uvula. We have resorted to 1 per cent Novocain for the immediate delivery, that is, when they do the episiotomy and the head is being expelled.

We have not had any questionnaires from the patients but definitely the pain is reduced. There is a certain amount of edema that prevents the obstetrician from repairing the episiotomy too tight at this time. Even though 4-0 catgut suture is used in repair of episiotomy, many will draw the sutures too tight. The edema caused by local infiltration prevents this to some extent.

DR. TAYLOR (Closing).—I wish to thank Dr. Galloway for his detailed discussion. I am sure that with local anesthesia success depends a great deal upon how much Demerol and scopolamine the patient has had as a predelivery analgesia. I know this also: that when we do not use general anesthesia we can give Demerol and scopolamine in very large amounts without causing fetal anoxia. I think it is the combination of general analgesia and anesthesia that produces difficulty in resuscitation. Obviously we can tell from the discussions

TABLE II. STAGE OF PREGNANCY WHEN CYST WAS DIAGNOSED

STAGE	NO. OF CYSTS	PERCENTAGE OF TOTAL
First trimester	16	64
Second trimester	7	28
Third trimester	0	0
Labor	1	4.0
Post partum	1	4.0
Total	25	100.0

After microscopic examination these cysts were found to be distributed as shown in Table III.

TABLE III. DISTRIBUTION OF ALL CYSTS

GROUP	NUMBER OF CYSTS
Functional	2
Neoplastic	10
Endometrial	2
Parovarian	1
Simple cysts	1
Unknown	9
(Not operated upon)	
Total	25

Both of the functional cysts were of the corpus luteum type. The ten neoplastic cysts are listed in Table IV.

TABLE IV. DISTRIBUTION OF NEOPLASTIC CYSTS

TYPE	NUMBER OF CASES
Monolocular serous cystadenomas	3
Multilocular pseudomucinous cystadenoma	1
Combined dermoid and multilocular pseudomucinous cystadenoma	1
Complex teratoma	1
Dermoid tumors	3
Papilliferous cystadenoma with early carcinomatous change	1
	10

The exact nature of the cyst was unknown in nine pregnancies since these were not removed and studied. In one pregnancy the cyst was 5 cm. in diameter when discovered, and remained unchanged and asymptomatic through a normal breech delivery. The patient was not examined again until the fourth month of her second pregnancy, two years later, when she had an 8 cm. cyst of the same ovary. When removed this revealed early carcinomatous change in a papilliferous cystadenoma. Another cyst occurred in conjunction with a hydatid mole, and regressed after curettage. Still another was discovered during labor and was displaced out of the pelvis allowing delivery to occur. This cyst was still present six weeks post partum, and until the sixth month of the second pregnancy which followed promptly. It could not be identified by careful examination immediately after the last delivery. The remaining five cysts likewise disappeared spontaneously in the fifth and sixth months. Since seven of these nine cysts disappeared spontaneously, they must be assumed to have been of the functional type. Adding these to the two known functional cysts it is apparent that nine (36 per cent) of the total series of 25 were functional.

Fifteen of the cysts in this series involved the right ovary, while nine arose on the left side. In one case it was not possible to determine the origin.

## PREGNANCY AND ADNEXAL CYSTS\*

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IN THE course of an obstetric practice one not infrequently encounters the problem of pregnancy and a coexisting adnexal cyst. The exact frequency of this combination is difficult to determine, since reports in the literature reveal variable findings (Table I). This report is based upon 25 pregnancies with associated parametrial cysts (24 were ovarian, and one was parovarian). They occurred in 23 patients over a thirteen-year-period including 7,598 pregnancies. Therefore, our incidence is one adnexal cyst in 304 pregnancies, or, if we omit the one parovarian cyst, we have an incidence of true ovarian cysts of one in 316 pregnancies.

TABLE I. INCIDENCE OF OVARIAN CYSTS IN PREGNANCY

AUTHOR	INCIDENCE
Litzenberg	1: 1,500 pregnancies
Mathieu and Holman	1: 102 pregnancies
Priest	1: 1,085 pregnancies
Falk & Bunkin	1: 2,500 pregnancies
(Average of reports in literature)	
Haas	
(All adnexal cysts)	1: 304 pregnancies
(Ovarian cysts)	1: 316 pregnancies

It is not surprising that there is considerable variation in the reported rate of occurrence of cysts during pregnancy, since this would depend not only upon the size of cysts included, but also upon the stage of pregnancy at the time of first examination. Realizing the difficulties of precise estimation of the size of pelvic structures, we have decided upon a lower limit of about 5 cm. We recognize that cystic enlargements of the ovary of less than 5 cm. occur not infrequently, but these are often difficult to distinguish from the normal ovarian variations, and therefore they are not included.

The duration of gestation at the time of initial examination influences the number of cysts reported because in early pregnancy functional cysts are more common. On the other hand, many cysts disappear spontaneously in the latter half of pregnancy and so will not be detected by late examinations.

As will be seen in Table II, nearly two-thirds (64 per cent) of these cysts were discovered during the first trimester and approximately one quarter (28 per cent) during the second. The fact that most patients are first examined before the end of the third month undoubtedly is a large factor in the high incidence noted during the first trimester. One cyst was discovered during labor, and one at the time of discharge examination 12 days post partum.

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TABLE VIII. ABORTION RESULTING FROM OVARIOTOMY

TYPE	NO. OF PREGNANCIES
None	12
Threatened	0
Actual*	2
Total	14
No operation or operation post partum	11
	25

\*Case No. 3.—2½ months; corpus luteum plus sedation; second postoperative day } Corpus luteum verum  
Case No. 8.—1 month; no treatment; third postoperative day } in both cysts

### Discussion

It was noted earlier that in one patient cysts of the same ovary existed in two successive pregnancies two years apart. When removed during the second gestation the cyst was found to contain early carcinomatous change in a papilliferous cystadenoma. If the cysts in these two pregnancies were actually but one persistent cyst, as seems likely, the question arises as to how long the carcinomatous change may have been present. TeLinde and Galvin,<sup>6</sup> Stevenson and Scipiades,<sup>7</sup> and Pund, Nettles, Caldwell, and Nieburgs<sup>8</sup> have all reported evidence to show that in cervical malignancy the neoplasm may remain in the early (intraepithelial) stage for several years. It would not be unreasonable to assume that the same latency may occur in ovarian malignancy, thus emphasizing the possible risk of being too conservative when dealing with persistent ovarian cysts.

There were nine cysts whose contents have long and generally been considered as irritating to the peritoneum. These include one cyst with papilliferous cystadenocarcinoma, three dermoid tumors, one combined dermoid and pseudomucinous cystadenoma, one multilocular pseudomucinous cystadenoma, one complex teratoma, and two endometrial cysts. The presence of such a high proportion of these tumors (9 in 25 cases, 36 per cent) is of importance from the treatment standpoint, and should receive due consideration in any individual case.

Counterbalancing the above indication for removal of the cyst is the fact that the same number of cysts (9 in 25 cases, 36 per cent) were found to be functional. While this group does not have irritating or proliferative contents, the cysts are subject to the other complications mentioned below and thus should not be considered entirely harmless. Our experience with this group of patients indicates that most functional cysts will disappear by the fifth or sixth month.

The complications which may befall an adnexal cyst during pregnancy have been stressed by many authors, including Litzenberg,<sup>1</sup> Mathieu and Holman,<sup>2</sup> Falk and Bunkin,<sup>4</sup> and Capone.<sup>5</sup> However, figures to support this emphasis are notably lacking. The complications mentioned include torsion, rupture, suppuration, hemorrhage into the cyst, and obstruction of the birth canal, and because of these Litzenberg states, "Ovarian cysts discovered

Symptoms referable to the cyst were few, and usually of vague nature (Table V). Thirteen of the patients with adnexal cysts had no important complaints. Of the twelve patients who did present symptoms, ten had discomfort of some kind. This was not well localized, and in no case was it severe enough to inconvenience the patient. Two patients had symptoms suggesting torsion of the cyst, and one, with a cul-de-sac cyst complained of dyspareunia. It is apparent that adnexal cysts seldom produce symptoms until they become large.

TABLE V. SYMPTOMS REFERABLE TO CYST

SYMPTOM	NO. OF PREGNANCIES
None	13
Discomfort	10
Symptoms suggesting torsion	2
Dyspareunia	1

Among the 25 pregnancies making up this series, there were no spontaneous abortions, and only three patients had bleeding or cramps suggesting a threatened abortion (Table VI). This makes the threatened abortion rate 12 per cent—not much different than would be found among pregnancies in general. It appears, therefore, that the presence of a cyst during pregnancy does not materially increase the risk of abortion.

TABLE VI. ABORTION IN PATIENTS WITH ADNEXAL CYSTS

TYPE	NO. OF PREGNANCIES	PERCENTAGE OF TOTAL
None	22	88
Threatened	3	12
Actual	0	0
	25	100

One of the chief problems in connection with the management of adnexal cysts encountered during pregnancy is that of abortions produced by ovariectomy. Consequently, various medications have been recommended with the hope of preventing loss of the pregnancy. In general, these agents have fallen into one of two classes, sedatives and hormones. The sedatives may be either narcotics or smooth muscle relaxers, such as Pavatrine. The hormone is usually some corpus luteum preparation, although recently stilbestrol has also been advocated. We have not been impressed with the value of any of these preparations in preventing spontaneous abortions, although there might be some logic in their use when the corpus luteum verum is removed or when the uterus must be manipulated unduly. As shown in Table VII, ten patients in this series were given no antiabortion therapy postoperatively, three patients received a corpus luteum preparation, and one received both corpus luteum and sedation. Eleven other patients either had no operation, or their cysts were removed after delivery. Table VIII shows that only two of the fourteen patients operated upon during pregnancy did actually abort. Both were operated upon during the first trimester, and the corpus luteum verum was present in both cyst walls. It would seem that the error in these cases was in the early operation rather than in the amount or type of medicine given.

TABLE VII. POSTOPERATIVE ANTIABORTION THERAPY

	10
None	3
Corpus luteum	1
Sedation and corpus luteum	11
No operation or operation post partum	25

*d. Cysts Discovered During Labor.—*

Cysts in the upper abdomen will seldom require removal until after delivery. Those lying deep in the pelvis, however, are likely to be obstructive and treatment cannot be delayed. Occasionally they may be dislodged and pushed out of the pelvis, permitting the head to descend. If this is not possible, and particularly if the cyst wall is thin (suggesting that it is neither a dermoid nor an endometrial cyst) one may puncture it through the vaginal apex using a small needle. If clear thin fluid is obtained a larger needle may be used to empty the cyst and thus permit delivery. The patient should then be observed closely post partum for recurrence of the cyst in which case it should be removed. If the initial needling reveals anything but clear fluid, the use of a larger needle is contraindicated by the possibility of spilling the cyst contents into the peritoneal cavity, and the patient will probably be best treated by cesarean section and removal of the cyst. Indeed, the latter course would seem preferable in all but the very rare case. The progress of labor, and the size, location, and consistency of the cyst must be taken into consideration and each case individualized.

*e. Cysts Discovered Post Partum.—*

These cysts may be regarded in the same way as any cyst not related to pregnancy. In other words, cysts of over 5 cm. diameter should be re-evaluated frequently, and if persistent, or especially if enlarging, they should be removed.

Careful thought given to the management of these patients will not only prevent a certain number of unnecessary operations, but will also time the required surgery to the best advantage for the patient.

**Summary**

Although the number of cases in this series is too small to permit drawing definite conclusions, the following points are brought out:

1. The coexistence of adnexal cysts and pregnancy occurred with a frequency of one in each 304 pregnancies.
2. Complications of these cysts, such as torsion, rupture, hemorrhage, or suppuration did not occur.
3. Obstruction of the birth canal occurred only once, and was readily overcome.
4. Nine of the cysts were functional while ten were neoplastic.
5. Teratomas, including dermoids accounted for five cysts.
6. Cysts occurring during early pregnancy do not seem to be an important cause of abortions.
7. Ovariectomy during early pregnancy does carry some risk of producing an abortion.
8. Operations carried out in the second trimester involve practically no risk of abortion.
9. A plan for the management of cysts discovered during pregnancy is presented.

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during gestation, labor, or the puerperium with very few exceptions call for surgical interference at once." A similar view was expressed by Capone. On the basis of our small experience reported here we are not impressed that the complications mentioned are of frequent occurrence, nor are we convinced that immediate surgical interference is frequently required. Instead, we prefer a policy of close observation, commonly deferring decision as to whether and when to operate in any individual case until time has permitted a fairer evaluation of the cyst and its probable nature and significance. This applies chiefly to the small cysts seen early in gestation. Of course, the larger ones are seldom physiologic, and their significance is more readily apparent.

While it is neither advisable nor possible to lay down any hard and fast rules for the management of these cysts in pregnancy, we believe the following policies to be useful and logical.

*a. Small Cysts Discovered During the First Trimester.—*

Unless such a cyst is causing symptoms requiring its immediate removal, we prefer to wait until the middle of the second trimester before making final decision regarding its removal. This policy allows time for the functional cyst to regress spontaneously, and also for corpus luteum function to be taken over by the placenta, thus minimizing the risk of removing a corpus luteum verum. Furthermore, as the uterus enlarges, the cyst may be drawn up out of the pelvis where it can no longer serve as an obstruction. It may then be possible to wait for final evaluation until after delivery, or if removal is still indicated, the operation will usually be easier and less traumatic because the cyst no longer lies deep in the pelvis.

X-ray study of the pelvis may be of value in indicating certain dermoid tumors which contain calcium deposits, although, of course, the absence of calcification does not rule out a dermoid.

The decision as to whether operation is necessary or not depends further upon due consideration of the data here reported which show that 36 per cent of these cysts were functional while about the same number (40 per cent) were neoplastic. Unfortunately, it was not possible to establish any dividing line between these two groups on the basis of size of cyst or age of patient. However, by the middle of the second trimester most of the functional cysts will have disappeared. Therefore, the majority of those persisting to or after this period of pregnancy are probably neoplastic, and removal is indicated.

*b. Cysts Discovered During the Second Trimester.—*

What has just been said with regard to cysts discovered in early pregnancy and persisting through the middle of the second trimester applies equally well to those which are first recognized in mid-pregnancy. These are in all probability neoplastic, since most of the functional cysts would have disappeared and with few exceptions their removal is in order unless they are small.

*c. Cysts Discovered During the Last Trimester.—*

Interference with wound healing due to overstretching of the abdominal wall, together with the proximity of labor may alter the situation somewhat when a cyst is first diagnosed late in pregnancy. Discretion must be used, and in general operation may wisely be deferred a few weeks until after delivery.



such a cyst through the cul-de-sac is, as Williams has said, "a dangerous and reprehensible procedure." Cesarean section and concomitant removal of the cyst is the safer procedure.

The general note of conservatism and individualization of the patient with adnexal cysts complicating pregnancy, together with the plan of management of these patients in the various stages of pregnancy, as stated in this paper, should be a valuable aid in our teaching and should inspire further investigation of this kind.

DR. HAAS (Closing).—There is very little I wish to add except to say that the pneumoperitoneum procedure was used at the University of Michigan many years ago and has been given up for various reasons. I do not see why pneumoperitoneography is a great advantage in this sort of case because these cysts are usually low in the pelvis where they are readily palpated without subjecting the patient to a somewhat complicated and uncomfortable procedure.

## Discussion

DR. EMMETT A. MECHLER, Denver, Colo.—The dangers of spontaneous abortion, sterility, and premature labor as a complication of adnexal or ovarian tumors have been *variously stated by Williams, Stander, Remy, McKarron, and others*. In the light of this series of cases, however, it would seem that adnexal tumors have little or no effect upon the pregnancy. Stander has mentioned that any ovarian tumor of 4 cm. or less in size should be treated conservatively and that only if the tumor enlarges during pregnancy should surgical removal be considered. Recently Falk and Bunkin, and Miller and Wilson have stated that 95 per cent of all ovarian cysts which are 5 cm. or less in diameter are functional cysts and that “these cysts are no longer looked upon as part of the complex group of ovarian neoplasms, but simply as enlargements that come about as a result of altered physiological behavior of the ovary”; and they emphasize that the cyst be followed and that surgical treatment be instituted only if the cyst changes in size or becomes symptomatic.

The high incidence of adnexal cysts described by Dr. Haas is due no doubt to the careful and accurate examination of patients during the first trimester of pregnancy and is an evidence of good prenatal care. There is no doubt that many patients of this kind go through a pregnancy and delivery with undiagnosed adnexal tumors and without symptoms or complications. Many of the published reports deal only with cases in which tumors are found at operation and do not take into account the question of functional cysts.

In a series of 8,000 deliveries over a period of fifteen years at the Colorado Medical Center, we were able to find seven patients who had been operated upon for adnexal cysts complicating pregnancy; an incidence of 1 to 1,100. Of these seven cases, three were simple cysts, three were pseudomucinous cystadenomas and one was a dermoid cyst. Three of the patients were operated upon during the first trimester of pregnancy with no ill effect upon the course of the pregnancy. Only one patient in the series had mild symptoms referable to the tumor. I mention these statistics, not because they offer much in the way of clarifying this problem but because, like so many of the published reports, they refer only to cases seen at operation and do not reflect the true incidence of these tumors as reported here today. Further studies of the nature made by Dr. Haas in this paper are needed to help us in a better understanding of many features of this problem. It is probable that the true incidence of ovarian tumors complicating pregnancy is the same as in the nonpregnant patient of the same age group. Pregnancy has less effect upon the clinical course of ovarian tumors than in the case of uterine fibroids.

In my private practice and clinical experience, I have been unable to confirm the finding of such a high incidence of functional cysts, and it seems that this matter should have further discussion. It is pointedly stated by DeLee, Stander, Heil, Williams, Irving, and others that an ovarian tumor when discovered during pregnancy should be removed as soon as possible. We have taken the attitude that any ovarian tumor complicating pregnancy should be removed or explored, but that operation should be postponed until the fourth or fifth month of pregnancy to minimize the danger of miscarriage.

Pedunculated uterine fibroids often simulate ovarian tumors in location and clinical manifestations, making a differential diagnosis difficult or sometimes impossible without resorting to exploration.

Although, as has been frequently stated, the most common symptoms associated with adnexal tumors are those resulting from torsion, hemorrhage, or suppuration, the real danger to the patient lies in the possibility of the tumor's being malignant or premalignant, or that the cyst contents might be irritating to the peritoneum in the event of a rupture or leak which would result in a serious peritonitis. It is impossible many times except in the case of some dermoid cysts which might contain radiopaque material, to differentiate these from functional cysts other than by surgical exploration and biopsy.

It is a rare clinical experience to encounter an ovarian cyst which obstructs the birth canal during labor; and it should be emphasized that reposition of the cyst to facilitate delivery is an unsatisfactory and possible dangerous procedure. Puncture with drainage of

In the usual case it is not necessary to resort to this test of labor. Rather, a trial of labor will usually suffice to demonstrate whether or not engagement can occur. By trial labor we mean from six to twelve hours of active labor, with pains at intervals of five minutes or less lasting from thirty to sixty seconds, and which are sufficient to produce progressive dilatation of the cervix.

### Material

Cases used in this report are all from our private practice during the past ten years. All women who had in the past delivered pregnancies of three months or more, all patients in whom there were intercurrent obstetrical or other complications which would have a bearing on the delivery, all multiple pregnancies, and all women who entered labor three weeks or more prior to the expected date of confinement were discarded. In all, the primiparous deliveries which met these requirements numbered 723.

In 661 women (91.3 per cent), the fetal heads were engaged as proved by rectal examination prior to the onset of labor, or when labor first commenced. Sixty-two women (8.7 per cent) had fetal heads which were floating at the onset of labor, and it is this group with which we are concerned. We have made no attempt to group our cases according to the clinical estimation of disproportion, and have not classified any evident disproportion as either "relative" or "absolute."

The average age of patients in this series was 21 years: the oldest was 42, and the youngest was 18.

Forty-seven of the patients (75.2 per cent) had gynecoid pelves. Six women (9.6 per cent) had generally contracted pelves. Two patients (3.2 per cent) had asymmetrical pelves. Three patients (4.8 per cent) had platypelloid pelves. Of the four patients remaining there was one each (1.6 per cent) of anthropoid, justomnior, justomajor, and undetermined type.

The largest infant delivered in this series weighed 9 pounds, 13 ounces (4,464 Gm.) and the smallest weighed 5 pounds, 3 ounces (2,355 Gm.).

Forty-eight of the infants (77.6 per cent) were in occiput anterior positions. Nine infants (14.4 per cent) were in occiput posterior positions, and five infants (8.0 per cent) were in occiput transverse positions.

The shortest labor in the series was  $6\frac{3}{4}$  hours, the longest 44 hours. Four patients (6.4 per cent) had labor shorter than 8 hours, 21 patients (33.6 per cent) had labors between 8 and 18 hours in length, and 23 patients (36.8 per cent) had labors of over 18 hours. Twelve patients (19.2 per cent) had what eventually terminated as trials of labor. Three patients (4.8 per cent) had no labor whatever, undergoing elective cesarean section.

In sixteen patients (25.6 per cent) the membranes ruptured spontaneously prior to the onset of labor. In seventeen women (27.2 per cent) the membranes ruptured spontaneously after the onset of uterine contractions in the first stage of labor. In nine women (14.4 per cent) the membranes ruptured spontaneously in the second stage of labor. There were fifteen women (24.0 per cent) in whom artificial rupture of the membranes was carried out in the first or second stages of labor for the purpose of facilitating a trial or test of labor. Five of these women were later delivered by cesarean section.

Of the sixty-two women with floating fetal heads at term, forty-seven, or 76 per cent, delivered from below, and fifteen, or 24 per cent, were delivered by cesarean section. In the patients who delivered vaginally eighteen women (28.8 per cent) delivered spontaneously, nineteen (30.4 per cent) were delivered with low forceps, seven (11.2 per cent) were delivered by midforceps, and 3 (4.8 per cent) were delivered by high forceps.

## THE FLOATING FETAL HEAD IN THE PRIMIPARA AT TERM\*

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**E**NGAGEMENT is the mechanism whereby the fetal presenting part enters the maternal pelvis. When engagement has occurred in vertex presentation the greatest diameter of the fetal head has passed through the pelvic inlet, and the lowermost portion of the fetal head is at or slightly above the ischial spines of the pelvis. In primiparas, engagement usually occurs several weeks before term. Exceptionally, a primipara is found at the onset of labor with an unengaged fetal head, and it is a study of this group of individuals with which this paper is concerned.

It is generally accepted and taught that a floating fetal head in a primipara at term, especially if there is overriding of the head above the maternal symphysis, is suspicious of, but not positive for, fetopelvic disproportion. A rather pessimistic attitude toward vaginal delivery in these cases is apparent, most obstetricians regarding them as potential sources of difficulty.

As diagnostic aids in estimating the chances of vaginal delivery in this particular group of women several clinical maneuvers have been listed. The one most commonly used is the Hillis maneuver which consists of fundal pressure to force the fetal head into the pelvis while rectal examination is carried out at the same time to determine the extent to which the fetal head may be made to engage. Müller's method is that in which the examiner seizes the brow and the occiput of the fetal head with his fingers through the anterior abdominal wall and makes firm pressure downward in the axis of the superior strait while an assistant carries out a vaginal or rectal examination to determine the degree of descent of the fetal head. The Kerr method has the advantage of not requiring an assistant, and is carried out by simultaneously doing a vaginal examination with one hand and with the other hand (using the Pawlik grip on the fetal head) forcing the fetal head into the pelvis in the axis of the superior strait. Pinard's method consists of bringing the fetal head into close proximity to the pelvic brim and then making strong downward and backward pressure upon it so as to force it against the promontory of the sacrum with one hand while trying to insert the fingers of the other hand between the symphysis and the anterior portion of the fetal head.

Test of labor is the final criterion of the ability of a woman to deliver from below. According to King's test of labor means that the second stage of labor has been reached, that the membranes are ruptured, and labor is allowed to proceed for two hours to determine whether molding and engagement can occur.

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twice that reported from the New York Lying-In Hospital.<sup>5</sup> Etiology of fever in six cases was endometritis, in one case pyelitis, and in one case hematoma formation in the episiotomy site. We feel that our high incidence of puerperal morbidity was due to the increased number of labors that were longer than average.

The fetal deaths occurred two and five days post delivery, both from intracranial hemorrhage. In the first case labor lasted about ten hours, and descent was steady and constant until the fetal head reached the perineum. Fetal death in this case was probably due to neglect in delivering the infant after it had reached the pelvic floor rather than to the trauma of its coming through the pelvis. The second infant was delivered by midforceps application after a hard thirty-hour labor and after two hours' complete dilatation with no progress. The baby's head was markedly molded, and it was very difficult to resuscitate. This death was definitely due to an error in judgment, as the mother had a mid-pelvic contracture as demonstrated by x-ray, but which was considered adequate for delivery from below.

### Comment

It is safest for the obstetrician to assume that fetopelvic disproportion exists when an unengaged fetal head is found in a primipara at term. Every woman who presents such findings should be regarded as a potential candidate for cesarean section, and should be treated accordingly. The course of labor and the prognosis for vaginal delivery cannot be predicted after one examination, for the etiologic factors causing unengaged heads are so varied and often so obscure that original impressions must be corrected as labor progresses. It is essential to re-evaluate each woman should lack of progress toward engagement be observed during early labor.

Trial of labor is indicated in the majority of these women. By the end of six to twelve hours of labor enough changes shall usually have occurred to dictate the need for interference or the lack of need for it. In only two of our cases was it necessary to resort to a true test of labor (as previously defined) to produce descent of the fetal head into the pelvis.

From both fetal and maternal standpoints it seems unreasonable to continue trials of labor to or over twelve hours. Tamis and Clahr<sup>1</sup> report a fetal mortality of 41.6 per cent in patients in whom trials of labor continued for more than twenty-four hours; the increasing fetal loss rate being due to the protracted labors, to intrauterine infections, and to difficult forceps operations. It has been argued, as far as the mothers are concerned, that these same women will deliver from below more easily with subsequent pregnancies, justifying sacrifice of the first child to avoid present and subsequent cesarean section. Such an attitude to us seems totally unwarranted, as much more is to be lost than is to be gained by such long and complicated labors.

If cesarean section must be done to secure delivery trials of labor over twelve hours increase the maternal risk, particularly if the membranes are ruptured and the classical section performed. At present the low segment double flap type section performed after twenty-four hours' trial of labor does not produce a much higher maternal mortality than that of vaginal delivery after the same length of time.<sup>1</sup> The Waters extraperitoneal section offers the highest degree of maternal protection afforded by any type of section, and should be chosen for neglected or overmanipulated cases. Cosgrove<sup>2</sup> indicates that the maternal risk is not appreciably increased even if thirty-six hours of labor have elapsed if the Waters extraperitoneal section is done. There is no doubt that these observations have resulted in an increasing number of vaginal deliveries in women in whom cesarean section is postponed.

In our observations the use of penicillin and the sulfonamides has somewhat widened the latitude of the time which may elapse during labor. The use

Fifty-eight of the patients had no unusual complications during labor or the delivery, but four patients (6.4 per cent) evidenced difficulty; the difficulties being one severe vaginal laceration, and three occurrences of fetal distress as manifested by passage of meconium and changes in the fetal heart rate.

Puerperal morbidity in this series was 12.8 per cent with eight patients having febrile postpartum courses. There was no maternal mortality. There were two fetal deaths (3.2 per cent) in the series, both occurring in the neonatal period, and both from intracranial hemorrhage. Both of these mothers had mid-pelvic contractions and should have been delivered abdominally except for errors in judgment.

### Discussion

The cesarean section rate in this series was 24 per cent which would substantiate the general apprehension with which the unengaged head in the primipara at term is regarded. Twelve of the fifteen patients were given an unsuccessful trial or test of labor before being subjected to surgery. In these twelve patients there were four gynecoid pelves, four generally contracted pelves, and one each undetermined type, anthropoid type, justomino type, and platypelloid type.

Three women were subjected to cesarean section without any labor whatever. One of these women had a markedly asymmetrical generally contracted pelvis with a conjugate vera of 8 cm. and a biischial diameter of 7 cm. The second woman had a generally contracted pelvis with a true conjugate of 8 cm. and a biischial diameter of 7.5 cm. with very prominent ischial spines indicating a more than moderate midpelvic contraction. The third woman had an inlet contraction with a conjugate vera of 8 cm. and a transverse diameter of 10 cm. associated with a straight sacrum, with x-rays at term indicating a marked disproportion between the size of the maternal inlet and the fetal head. Only in these three cases did x-ray demonstrate an absolute indication for cesarean section, and then the x-ray was used to confirm our clinical findings, not to make the original diagnosis of fetopelvic disproportion.

The seven patients in this series delivered by midforceps application gave us a midforceps incidence of 11.2 per cent. Indications for the application of midforceps were fetal distress in two cases, and lack of progress after two hours in the second stage in the remaining five cases. In one of the seven patients the fetal head was in an occiput transverse position, and in one case the fetal occiput was posterior.

Three patients (4.8 per cent) were delivered by high forceps application. Indication for all three operations was lack of progress after too long procrastination safely to permit a cesarean section. In reviewing these cases it is quite apparent that all three women would have been better off to have been sectioned despite the fact that none of the mothers or babies were lost.

From this series it would appear that position of the fetal head has little or nothing to do with lack of engagement. In only one of the nine patients in whom the fetal head was occiput posterior was cesarean section necessary for delivery, and in the five patients where the occiput was transverse none were brought to section. Thus fourteen of the fifteen section cases had the infants in an occiput anterior position.

Infant weight seemed to have little to do with the outcome in this group of cases. Weinberg and Seadron<sup>5</sup> have previously pointed out that there is no constant relationship between fetal weight and head diameter, and this too has been our experience. In the group of women who were subjected to cesarean section only two infants were larger than 8 pounds (3.650 Gm.), while sixteen women delivered larger babies from below.

Eight of the women in the entire series had febrile postpartum courses, an incidence of 12.8 per cent. Thus, our incidence of morbidity is more than

### Conclusions

The primipara with an unengaged fetal head at term should be regarded with suspicion, and the same woman in labor should be regarded with apprehension.

In our experience x-ray measurements of the pelvis will seldom demonstrate absolute indication for cesarean section in primiparas with floating fetal heads.

Every primipara should be given an adequate trial of labor unless pelvimetry, clinical and x-ray, proves this unwarranted.

In our experience a twelve-hour trial of good labor without descent of the fetal head should be deemed adequate, after which cesarean section should be done without procrastination.

More than one-third of the primiparas in this series who reached term with an unengaged fetal head had some degree of midpelvic contraction. In many of these women, after engagement occurred, the midpelvic contracture led to extremely difficult forceps operations which should best have been eliminated in favor of cesarean section.

A cesarean section rate approaching 40 per cent in a series of primiparas with floating heads at term would be more conservative than our reported rate of 24 per cent when the possibilities of fetal injury and death, as well as extensive damage to the vagina and pelvic floor and their aftermath, are considered.

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### Discussion

DR. A. W. DIDDLE, Dallas, Texas.—Drs. Auer and Simmons found that most of their primiparas at term with floating fetal heads usually could be delivered vaginally. In other words an unengaged fetal head in a primipara in early labor is not alone indication for cesarean section. To the contrary, they were of the opinion some of their patients with floating fetal heads would have been treated better by section because they had a midpelvic contraction and suffered with an increased puerperal morbidity and had a greater fetal loss than normal.

Using Drs. Auer and Simmons' criteria for selection of patients, the relationship of the floating fetal head to the outcome of labor was analyzed for 276 consecutive primiparas delivered at Parkland Hospital in Dallas, Texas, in the first six months of 1948. Twenty-two, or nearly 8 per cent, were admitted in early labor with the fetal head unengaged while among the other 254 the fetal head was engaged. Discussion concerns the 22 women with unengaged fetal heads. All of these had a vaginal delivery. All babies and mothers survived. None of the babies was premature or postmature. All labors were under twenty-five hours in length except two. These were thirty and thirty-one hours in duration and associated with a brow presentation. Delivery was spontaneous for all except six patients.

of these drugs has, in addition, reduced the occurrence and severity of intra-uterine and peritoneal infection; diminished the need for extraperitoneal section or the Porro operation, and diminished infant mortality. It has been our custom to administer these drugs where delivery is delayed after rupture of the membranes, to patients in poor or protracted labor without rupture of the membranes, to patients with intercurrent infections, and before and after cesarean section. It must be remembered that these aids cannot replace good clinical judgment. Labor must not be prolonged unnecessarily in the hope that poor judgment can be compensated by good drugs.

In recent years the x-ray has become an important aid to clinical judgment in the handling of these cases. Many methods have been proposed for measuring the diameters of the fetal head and the maternal pelvis, and in estimating the fit between the two. Williams and Phillips<sup>9</sup> report that 94 per cent of abnormal deliveries due to disproportion were predicted in advance by x-ray, and so it should be possible for the obstetrician-radiologist team to reach a high degree of reliability of prediction in primiparas with unengaged fetal heads. However, we feel that this method should be considered an adjunct only, as in only three of our cases did x-ray prove absolute indication for section, and in the other twelve women subjected to section the x-rays were reported as indicating a pelvis adequate for delivery from below. It has been our practice to use x-ray measurement routinely in patients in whom there was any suspicion of inadequate pelvic size, or unusual pelvic configuration.

Attempts to shorten the first stage of labor by hydrostatic bags, Dührssen's incisions, or any other form of accouchement forcé are contraindicated as they have no bearing whatever on the factors originally responsible for the unengaged fetal head. In one of our cases Dührssen's incisions were used, but only after engagement had occurred.

The membranes are a factor in descent of the fetal head in the pelvis.<sup>10</sup> Intact membranes may occasionally retard engagement when there is no true disproportion present, and artificial rupture of the membranes will hasten descent in these cases. In women with apparent disproportion it is well to leave the membranes intact as lack of engagement here is not considered the result of the presence of amniotic fluid.

Banister<sup>6</sup> reports on a series of women who had medical and surgical induction of labor prematurely for apparent fetopelvic disproportion. In his series the fetal mortality was 12.6 per cent, the maternal mortality 0.13 per cent, the maternal morbidity 4.0 per cent, with failures and ultimate cesarean section 3.2 per cent. He feels that this method of handling fetopelvic disproportion has come into unwarranted disrepute. We have had no first-hand experience with the method, but it appears that with the high fetal mortality that he and others (Peel) report premature induction has no place in the management of the primipara with small pelvic measurements or apparent fetopelvic disproportion.

The elderly primipara and the woman of long-standing relative sterility pose a problem for obtaining a living child in good condition. These women should be treated exactly like any other primipara except that the trial of labor should not be allowed to continue too long particularly if the membranes are ruptured or the labor is weak and ineffectual.

In our series of floating heads more than 33 per cent of the women studied had midpelvic contracture of greater or lesser degree. Most often the midpelvic contraction was not associated with any alteration of the pelvic inlet from the normal. We are unable to offer any reasonable explanation for the fetal head found floating where there is no mechanical barrier to its passage at the inlet, but where there is midpelvic contraction. The absence of engagement in this situation is a problem deserving further study.



answer to one of the questions, we called a case successfully concluded when we ended up with a living mother and a living baby. Although I cannot give you the figures because we have made no attempt to follow up the cases, I am sure that a great number of these babies that were born to mothers with midpelvic contractions had residual intracranial disease, and many of these mothers had extensive repairs of their pelvic floor and vagina which were due to the laceration caused by the forceps particularly in the mid- and high variety. Incidentally, I do not believe that there is any place in the practice of good obstetrics for high forceps delivery. I agree that a time limit cannot be placed on the length of labor of any one individual. It depends entirely upon the individual case, but we do feel that twelve hours of labor is a fair average. Some of these patients were sectioned before the twelve-hour period, and some of them long after a twelve-hour period.

In the future I do not want even to consider a Waters' or any other type of extra-peritoneal cesarean section in my own private practice. I feel that these operations are wonderful in clinic practice for neglected cases, but I don't want to be responsible for a neglected case in my own private practice, and for that reason I don't care to do extra-peritoneal cesarean sections. In the future we intend to take advantage of the hindsight that we have gained by experience instead of the foresight that we have depended upon up until now, and in the next ten years I don't expect to say, "I wish I had done a section on that patient," nearly as often as I have in the past ten years.

Among half of these a low application of forceps was made electively and for the other half a mid (two cases) or a high (one case) application of forceps was done for a prolonged second stage. The indication for the midforceps was, respectively, a transverse arrest due to uterine inertia and a persistent occipitoposterior position in a patient with a borderline midplane pelvic contraction. The woman subjected to high forceps application also had a brow presentation and had to have a manual removal of the placenta. In this instance, the mechanism of labor was interfered with by an intramural fibroid located in the lower uterine segment. In spite of the favorable outcome for both mother and baby, treatment would have been effected better with abdominal delivery. There would be room for argument regarding the advisability of sectioning the patient with the persistent occipitoposterior, but assuming this were the procedure of choice, only one in eleven patients should have been sectioned. Roentgenographic studies showed five, or nearly 23 per cent, of the twenty-two parturients had either an inlet or midplane contraction or a generally contracted pelvis. All had a normal delivery except the woman with the persistent occipitoposterior.

My obstetrical experience has led me to develop three opinions regarding the care of the primipara at term with unengaged fetal head. One, roentgen study of the pelvis is a valuable adjunct in predicting the outcome of most labors but it should not supplant clinical judgment. Occasionally there is the case where a trial of labor is the only method available to determine whether or not vaginal delivery can occur. Second, if a primipara goes into labor at term with a floating fetal head and with questionable pelvic disproportion a trial of labor of twelve to eighteen hours should be given. If after twelve hours abdominal section appears to be the procedure of choice, section should be done through the lower uterine segment. If more than twelve hours have elapsed and section is elected, one of the extraperitoneal procedures is preferred. It is apparent that most of us have done traumatizing vaginal deliveries where abdominal delivery should have been used. Yet, as an over-all picture, I am not ready to agree with Drs. Auer and Simmons that the cesarean section rate should be as high as they suggested for primiparas at term with floating fetal heads. Third, and to the contrary, there is agreement with the essayists that patients with prolonged labors and operative vaginal trauma suffer more often with puerperal morbidity and have a greater fetal loss than do those with labors that are not prolonged. The increased fetal mortality is often due to fetal infection acquired in utero (Douglas, R. G., and Stander, H. C.: *AM. J. OBST. & GYN.* 46: 1-19, July, 1943). It is important to know that penicillin and sulfonamides cannot always be depended upon to prevent fetal infection in utero.

DR. GEORGE KAMPERMAN, Detroit, Mich.—I think everyone who practices obstetrics will agree that these cases are problems, and a great deal of judgment is certainly necessary. Often after we deliver our patient we wish we had done something else. When we deliver a patient vaginally after a long labor and with much traumatization, sometimes with an unfortunate result as far as the fetus is concerned, we may feel perhaps we should have done a section. On the other hand, if we do our sections early, I think many times we destroy our evidence. The fact that we have done a section does not necessarily mean that a patient could not have been delivered from below. It may give us a great satisfaction to know we have delivered the patient successfully but yet we have not the evidence that those patients cannot be delivered vaginally.

Personally, I do not feel that I can set a definite number of hours as to how long a trial of labor should be. It is not a question of exactly twelve hours or even eighteen hours. It is a question of the type of labor that is going on while we are giving that trial, and I have on many occasions with these high presenting parts allowed patients to go longer, and find that a little extra time will sometimes cause the head to descend. So I believe we must take many factors into account, not only the question of time but also the type of labor.

DR. AUER (Closing).—I want to emphasize the fact that ours was a very carefully selected group of primiparas, none of whom had pelvic tumors nor any evidence of intercurrent medical disease. Each and every one of these was an occipital presentation. In

Aside from the discomfort of carrying extra pounds during pregnancy the only valid argument so far adduced for limitation of weight gain is that any excessive net gain at the end of the puerperium is unsightly and undesirable. Hence, it is argued, the tendency toward obesity must be curbed and the treatment of obesity undertaken during pregnancy.

Since pregnancy and the puerperium, which is here considered to extend to at least three months post partum, occupy a full year, it is pertinent to consider what the nonpregnant woman may be expected to gain in any year. From a study of the tables prepared for the Metropolitan Life Insurance Co. by Dublin and Marks<sup>1</sup> it appears that between age 20 and 30, the average woman in the ordinary height ranges will gain just over 1 pound per year. Furthermore, since most pregnancies involve young women in their early married life, the effect on weight gain of marriage alone must be included. Competent statistics quoted in a personal communication from Dr. Louis I. Dublin reveal the fact that between age 18 and 30, married women without children weigh 1.12 pounds more on the average than single women. Thus, being a year older and being married add to a woman's weight, regardless of her being pregnant.

### Material

This study involved a series of 226 consecutive, unselected private cases. This number proved to be a significant sample (between the .01 and .001 significance level, using Student's *t*-rule and Fisher's *F* ratio test) by comparison with the series presented by Chesley<sup>2</sup> in 1944, involving 12,000 cases. No restrictions were placed on the diet of any of these women other than a reduction of salt intake whenever edema was noted in the latter months. Each received a multivitamin capsule daily throughout pregnancy and added calcium after the twenty-fourth week; whenever the hemoglobin fell below 12.5 Gm., ferrous sulfate was prescribed. Thus, from the point of view of calorie intake the technique might be described as "free-feeding"; that is, a matter of the individual woman's choice. These women were all in a moderate to high income group, and the diets were adequate.

There was no case of toxemia of pregnancy other than a single mild chronic nephritis, and a few transient elevations of blood pressure or albuminuria insufficient to warrant any treatment. Three infants were stillborn, the causes being: abruptio placentae, asphyxia due to cord tight about the neck, and a prolapsed cord in a large breech. One neonatal death occurred, due to erythroblastosis fetalis in a woman whose Rh antibody titer rose gradually to 1:2056 before cesarean section was done at the thirty-second week. There were 21 other premature infants, all of whom survived. There were no malformations other than two with clubfeet, one very mild and the other moderate, both corrected satisfactorily. None of those cases was correlated in any way with a significant weight gain deviation from the average.

The average total gain in weight was 24.4 pounds (standard deviation, 8.7) and the average postpartum gain was 2.0 pounds (standard deviation, 6.3). Thus it may be said, with better than 100 to 1 certainty, that if one desires the average pregnant woman to gain just under 25 pounds and to retain at the end of three months only 2 pounds (what she might well have added to her weight even if not pregnant), she may be allowed an unrestricted calorie intake.

But the individual woman is not necessarily average. A study of the distribution curve demonstrates that about two-thirds of all pregnant women on an

## FREE-FEEDING PREGNANT WOMEN\*

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THIS study was undertaken to note whether any advantages accrued from the currently popular custom among obstetricians of trying to restrict the gain in weight during pregnancy to 25 pounds. The investigation included questions such as whether or not a significant relationship exists between the total gain in weight during pregnancy and weight at the end of the puerperium and of what elements the gain in weight, both total and net, consist. Consideration was then given to an analysis of the causes of the gain in weight, whether more harm than good resulted from a restriction of the caloric intake, and the best methods of reducing the net gain to a minimum.

The original arguments for limitations of weight during pregnancy were based on the idea that with a lower caloric intake the size of the child would be reduced and labor would be easier. Whether the delivery of a puny, malnourished newborn was desirable did not enter the scientific discussions at all. These arguments disappeared from the literature in the late 1920's when it was recognized that even in countries which had experienced starvation during World War I and the following years, the average weight of babies was not lowered significantly, certainly not enough to have any real effect on the ease of labor. And there was no doubt that women starved sufficiently to have smaller babies died in greater numbers than their more fortunate sisters with ample diets and a reserve of strength to meet infection, hemorrhage, and shock.

The argument for restricting the diet of pregnant women has been resumed in the past five years with sweeping but poorly documented claims that with a limited weight gain there is a lower incidence of abortion, toxemia, prematurity, stillbirths, neonatal deaths, and malformations. The inescapable inference is that excessive weight gain is the cause of these difficulties; although they sometimes are associated with a high weight increment, there is no evidence of any relationship other than a common origin. Some pathologic process produces toxemia, which, as all textbooks state, is often manifest by an excessive weight gain; in toxemia there is a higher incidence of prematurity, stillbirth, and neonatal death. It should be obvious that these complications will be found more often among the women who gain excessively, but not *because of it*. One of the more serious harmful effects of this sort of thinking has been the hysterical fear engendered in some impressionable women who have read lay transcripts of published articles with this argument. Upon discovering that their pregnancy gain is a few pounds above the average they become convinced that they are doomed to have a stillbirth or a malformed child or convulsions, at least.

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The application of the same technique to the relationship of starting weight and net gain, i.e., retained weight, resulted in a correlation coefficient of  $-.12$ . Interpreted clinically, the evidence shows that three months post partum there is a slight tendency for heavy women to retain less of their pregnancy gain than do slender women. One might say philosophically that Nature tries during pregnancy to correct over-or-underweight.

Chesley<sup>2</sup> found the average pregnancy increment to be 24.0 pounds (standard deviation 10.8). In analyzing just what this gain in weight comprised he found, in 958 cases studied, that the products of conception, that is, the baby, the placenta, and the amniotic fluid, averaged 11 pounds. He calculated the rest of the gain in weight to consist of an increase in the uterus amounting to 2.5 pounds, the breast, 3.0 pounds, and the circulating blood volume, 3.5 pounds, a total of 9 pounds. In addition he estimated an increase in interstitial water and protein amounting to 4.5 pounds. Whether or not these latter calculations are accurate, as questioned by Dieckman,<sup>4</sup> Chesley did demonstrate that during pregnancy there was a positive salt and water balance, i.e., a retention, and that during the puerperium this balance became markedly negative. He found the loss of water in the six weeks post partum to average 13.2 pounds, of which 5 pounds were lost in the first six days.

It is well established that the salt and water balance is associated with, and probably controlled by, the endocrine system, chiefly the estrogen component. An analogy of what goes on in pregnancy may be found in the work of Thorn and Emerson<sup>5</sup> who found that 24 of 50 normal, nonpregnant women gained 2.2 pounds or more in the week before menstruation, and lost that weight right after menstruation by diuresis and excretion of salt. In eclamptogenic toxemia the edema and excessive gain in weight may well represent a profound disturbance of this endocrine-electrolyte-water mechanism, particularly as such excellent results are obtained in the mild cases by simple withdrawal of salt from the patient's diet. Also, in the frank cases of severe toxemia of pregnancy the promotion of diuresis is an essential part of the treatment.

One cause of excessive gain in weight during pregnancy, therefore, is an abnormal retention of water in the tissues, which, if accompanied by certain other symptoms and signs, is a manifestation of toxemia of pregnancy. If the pathologic process is severe, its end point is eclampsia, but if the process is very mild the only effect on the woman that is demonstrable may be the disturbance in the water balance which shows up in her weekly weight. The treatment must be directed at the cause or the focal point. In this type of excessive weight gain, if any concern is felt, withdrawal of salt from the diet, rather than restriction of caloric intake, is the logical therapy. This gain in weight, however, as was demonstrated by Waters,<sup>6</sup> is easily lost during the puerperium. The woman is almost invariably back to her starting weight by the time she is menstruating regularly and her endocrine status is once more that of the nonpregnant type.

The other chief cause of excessive weight gain in pregnancy is simple obesity. A woman gets fat because she eats more than she needs for her particular metabolism and activity. A very few women, creatures of habit, may conceivably continue their usual caloric intake despite the restriction on activity that pregnancy imposes. But this is counterbalanced by the demands for a greater caloric intake due to the growing fetus.

Why the pregnant woman eats more than her body needs is the basic problem, and intelligent handling of it requires the understanding that the origin of obesity is psychological. The pregnant woman suffers acutely from insecurity and anxiety over such things as her own survival, whether or not her child will be healthy, whether she can successfully meet the seemingly terrific responsibility of caring for the child, the new social adjustments she will have to make in her way of living, and the not inconsiderable added financial burden. Other

unrestricted diet will gain between 16 and 33 pounds, and three months post partum will weigh between 4 pounds less than 8 pounds more than they did before becoming pregnant. Is there any correlation between the total gain and the net gain or is the net gain due to other factors? This is important in deciding whether to make any efforts to restrict the gain in weight during pregnancy.

For example, of two women who gained 46 pounds, one retained 10 pounds, the other only 2 pounds; and of 47 women who gained 22 pounds, four emerged 10 pounds heavier than when they started, but three emerged 10 pounds lighter; and of ten women whose total gain was only 10 pounds, one had a net loss of 16 pounds and one a net gain of 18 pounds. Or, looking at it the other way, of two women who were 18 pounds heavier a year after becoming pregnant, one had gained 14 pounds during gestation, and the other 43 pounds; and of 23 women whose net gain was under 2 pounds, 40 gained less than 24 pounds, and 43 more than 24 pounds. The distribution of net gains and total gains in relation to each other is shown in Table I.

TABLE I. DISTRIBUTION OF CASES; RELATIONSHIP OF NET GAIN AND TOTAL GAIN

		TOTAL GAIN (POUNDS)												
		4	8	12	16	20	24	28	32	36	40	44	48	52
NET GAIN (POUNDS)	28													
	24								1					
	20										1			
	16			1							1			
	12				1		1	1	3	3	2			
	8				1	4	6	3		1	1*	1		
	4		2	1	5	7	2	5	9	3	1		1	
	0		2	1	5	10	22	20	8	11	2		1	1
	-4		1	1	3	8	8	4	5	2				
	-8	1		2	3	4	3	2	1	1				
	-12			3	3	1	3							
	-16	1	1		1									
	-20	1	1	1										

The correlation coefficient between total gain and net gain in this series was .5, with a standard deviation of .05. (Translation to z values of .54 and .067 fixes the coefficient of correlation for two-thirds of all sampling that may ever be made as between .493 and .629.) This means that there is a valid and significant positive correlation between the total gain during pregnancy and the net gain at the end of the puerperium. But the correlation is low, and mathematically, using the coefficient of determination (r squared), it can be stated that not quite 25 per cent of the net gain three months post partum is related to the total gain during pregnancy. The rest of the net gain is due to other factors such as starting weight, body build, individual water metabolism, metabolic changes initiated or aggravated by pregnancy, and the individual tendency toward obesity.

The correlation coefficient of the total gain in weight and the original starting weight was -.121. This small negative correlation merely records statistically that there is a very slight tendency for heavier women to gain less during pregnancy than the lighter women. This confirms the conclusions of Beilly and Kurland<sup>3</sup> that "the size of the mother influences the weight gain during pregnancy; light women show a larger gain, and heavier women a smaller gain."

If treatment of the increased weight during pregnancy is deemed desirable it should be accomplished by superficial psychotherapy, rather than either an arbitrary restriction of food intake or an unsupervised diet list. The obstetrician can accomplish his aim more successfully, safely, and without trauma to the patient by spending a little time allaying her fears, explaining the entire process of pregnancy, parturition, and the puerperium to her, by debunking the lay press and the old wives' tales, by universalizing her ideas and emotional swings, by giving her a genuine feeling of the support, availability and responsibility of the obstetrician, by building up the patient's confidence in herself, by strengthening her more mature tendencies, and by orienting her to a forward-looking viewpoint. The fewer modifications made in her ordinary routine life, the less disturbing is the entire pregnancy, including even the parturition. Eating is so important a part of a person's emotional life, that the women's habits in this respect should be changed least of all, unless toward a fuller, more adequate, more enjoyable, and more satisfying diet.

### Summary

1. In a study of 226 cases, a sampling shown to be statistically adequate, no restrictions on caloric intake were placed during the entire pregnancy. The average weight gain was 24.4 pounds (standard deviation 6.7) and the retained weight, or net gain, at the end of three months post partum was 2.0 pounds (standard deviation 6.3). The correlation between the total gain and the net gain was low, the coefficient being only .5, indicating that only 25 per cent of the retained weight is related to the number of pounds the woman gains during pregnancy.

2. Statistics demonstrate that the average woman gains about 1 pound a year regardless of pregnancy, and that the married state increases a woman's weight by about the same amount, married women without children weighing about 1 pound more than unmarried women.

3. Pregnancy has a tendency, although very slight, to correct over- or under-weight conditions, heavy women gaining less and retaining less weight than slim women who tend to gain more and retain more.

4. A gain in weight in excess of the standard is due to either or both of two conditions: an exaggeration of the positive water balance or developing obesity.

5. Excessive weight gain due to water retention may be a manifestation of subclinical toxemia of pregnancy, and it disappears completely during the late puerperium. Reduction of the caloric intake of such patients will have little effect on this cause of weight increment, and may do harm if necessary protein is withheld in proportion to the storage of water in an effort to keep the weight down.

6. The incipient or developing obesity is a psychologic problem, and may be a compensation for insecurity or anxiety either induced or intensified by the pregnancy. Deprivation of the oral satisfaction of eating merely compounds the basic psychologic problems, particularly if done in a dominant, threatening, or punitive manner.

7. Control of the overeating by a diet list and instructions is effective only if the psychologic drive to eat is slight. The explanation and attention given to obtain the patient's cooperation constitute a form of psychotherapy, and in simple cases may be all that is necessary.

worries include the potential loss of her husband's love or fidelity, the ever-present, ever-growing distortion of her own beautiful body, and the fear that the pregnancy will leave her less attractive. The pregnancy is a dramatic reminder that she is about to take the momentous step from one generation to another, leaving the era of dependency and entering the one that presumes full maturity. With motherhood she becomes identified with her own mother, with whatever unhappy ideas this may evoke. Even without going into the deeper levels of motivation, such as possible unconscious death wishes toward the child, guilt feelings, and a compensatory attempt to feed the child amply by "eating for two," one can understand how at the moment when she feels sorry for herself, a big chocolate fudge sundae carries her back to the blissful days of her carefree childhood. It gives her as much relief from her psychic pain as an analgesic drug for her physical pain.

What is the treatment for obesity or the treatment to prevent the development of obesity? And is pregnancy the right time to treat it? One method is to tell the woman emphatically that she must not gain more than 20 or 25 pounds, to castigate her if she shows a tendency to overeat, to tell her arbitrarily to restrict her food intake or to cut out the starches and sweets that give her the most satisfaction, to become the stern, punishing father-figure, or to scare her with quotations from the current literature, both professional and lay, that women who gain have a higher incidence of stillbirths or deformed children. This method is simple, takes very little of the doctor's time, and gives him a sense of great importance. But it also increases the woman's anxiety and gives her guilt feelings; she wants to eat even more, just as the child, punished for sucking his thumb, solaces himself by sucking his thumb. This is the woman who requires tremendous doses of analgesics during labor, who has a long, agonizing labor, and who goes down in the statistics to prove that excessive weight gain produces a long, hard labor. If she obeys the doctor, humbly and unhappily, she cuts down on the food she doesn't particularly care for, often depriving herself of necessary protein, minerals, and vitamins.

Another method is to give the woman a diet list and a short course in dietetics, with frequent review of her eating habits and interrogation of her food intake. All studies indicate that the qualitative aspects of diet are more important than the total caloric intake, and the best work in this connection is summarized by Bertha S. Burke<sup>7</sup> who states: "Adequate diet is a significant factor in reducing the incidence of toxemia, prematurity, and stillbirth." But this method requires research enthusiasm, time, and cooperation. Few doctors and fewer clinics have the facilities and time to do this properly, and a printed list and a few brief words at the first visit are inadequate. The women who cooperate are those whose drive to overeat is slight, and those hardly need the regimen. Adequate time and patience spent with those who do need it, in order to obtain their cooperation, actually amounts to psychotherapy.

The successful treatment of obesity in general is psychologic, as was shown by Nicholson<sup>8</sup> who divided 93 cases into four groups. Of 20 patients given nothing but thyroid with or without amphetamine, none was cured. Of 35 patients put on a strict reducing diet and nothing else, only 9 were cured, even while still on the diet. But of 38 patients treated for their obesity by psychotherapy alone, 26 remained cured permanently.

The situation is exactly the same during pregnancy, except that the pregnancy, with its attendant psychologic disturbances, is the cause of the overeating which leads to the obesity. In most cases, once the woman finds that she has survived the pregnancy, has a lovely baby that is admired by all her friends, has retained her husband's love, has proved herself capable of caring for the baby, has compensations for her restricted social life, has acquired a new dignity as a mother, she has lost her need to stuff herself and will lose her extra weight without further treatment.



along the paths of healthful living. As obstetricians it devolves upon us to inoculate a spirit of cooperativeness among the women who come to us for advice and care on their prospective motherhood. If they gain sufficient understanding of the principles involved there will be no hesitancy on their part in following our advice.

Good psychosomatic medicine during prenatal care is not necessarily a matter of wiping out frustrations; rather it is an attempt on the part of the obstetrician to condition the prospective mother toward acceptance of the realities of life as it is, and toward wholesome adaptation to the changes of living when the baby arrives.

DR. SINGLETON: I think Dr. King is to be commended for the care he has used in this study and in his observations and for the keen sense of humor that has carried him through in his contacts with his patients. I have been interested in the value of a high protein diet in the early part of pregnancy with the end in view of getting a better breast development that might lead later to more satisfactory lactation. I would like to enlarge some on Dr. Stacy's question to ask Dr. King also whether he feels that persistence in breast feeding leads to a better endocrine glandular readjustment, a more rapid return to normal weight and a more satisfactory emotional readjustment.

DR. RALPH REIS, Chicago, Ill.—Let me call attention to the fact that Dr. King and the discussants are three middle-aged men who are very slim and have no obesity problem. As one who has struggled against psychosomatic obesity for some fifty years this paper strikes a very deep note. In my resident days I weighed 240 pounds. And the only time I will exceed my rigid diet today—and it is a carefully restricted diet with the exception of alcohol—is when I have had a particularly frustrating day in the office. Then I will suddenly find myself at the soda fountain on the main floor eating that same double chocolate sundae that Dr. King talked about.

So I am very sympathetic to Dr. King's work, and I am very appreciative of his calling to our attention the psychosomatic angle. I think many of the previous reports have influenced us into browbeating our women into restricting their caloric intake. We have confused in our own minds two groups of women, first the women who overeat because they just overeat and then gain too much, and second the women who gain too much because they have an oncoming or existing toxemia. I think we must separate those two groups. There is no question that the toxemic woman frequently first manifests her toxemia by excessive weight gain. Such weight gain must be rigidly controlled.

My colleague in the office has attempted to control weight gain rigidly among his own patients while I have allowed my patients to go on pretty much their own way. To date we have found no difference in the two groups, and I am convinced that there is no value in rigid weight control. I feel that such weight control is not only unnecessary but useless.

DR. KING (Closing).—To answer Dr. Stacy, all the cases were private, belonging to a moderate to high income group, which presumed that their diet was adequate, certainly as far as any economic restriction might be placed up on it. The average American diet has been criticized a great deal, but it is a personal observation that all of us eat pretty much what we should unless we are confused by fads, or what cousin Tillie learned from her doctor, or by some sort of extraneous influence on our food habits.

I wish I could give the exact figure of the percentage of women who nursed their babies, but I don't have it. Dr. Singleton extended that question, and I will say this: That the women who nursed their babies took a little longer to drop their weight back to pretty much normal, but they were happier doing it. I am in favor of women nursing their babies although more because of the psychologic effect, as I think the woman is entitled to the satisfaction she gets from a strictly maternal process. Not being enough of a pediatrician to know whether or not it helps the baby, I suspect that the baby is more comfortable with all of the accessory elements that go with eating. All of us prefer to eat under pleasant circumstances, where it is warm and comfortable, off a tablecloth of

8. Superficial psychotherapy, usually adequate, is within the scope of most practitioners of obstetrics, and consists of giving the patient true confidence in her doctor and in herself, allaying her fears and anxieties, and establishing in her a mature, optimistic orientation.

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701 UNION CENTRAL BUILDING.

### Discussion

DR. RALPH LUIKART, Omaha, Neb.—The principles of psychosomatic medicine are so well accepted that no sane physician can afford to neglect their application in his daily contact with patients. Their utilization in prenatal care to the advantage of all concerned is a fact no one can deny. However, as is so universally true of human nature in general, the danger of carrying sound principles too far must be recognized. I am wondering, for example, whether Dr. King's fears of frustration incident to dietary control are not based on supposition rather than fact. I have utilized the high protein, low carbohydrate and fat diet for almost twenty years, and I have not observed a single woman who has shown evidence of somatic or psychic disturbances as a result of this dietary control. I have had a few patients who considered the regimen unacceptable and who by their own decision, or at my suggestion, changed physicians, but I have yet to see the first patient who takes her dietary directions seriously enough to interfere with her physical or emotional welfare.

All of us who have had experience with dietary restrictions during prenatal care have found it beneficial and have observed a reduction in the incidence of maternal and fetal mortality and morbidity. Although axiomatically every pregnant woman is a potential candidate for toxemia, in a series of 1,400 consecutive pregnancies on dietary limitation which I reported in 1947, there was not one case of toxemia, while in the controls there was an incidence of 10.4 per cent.

I have the utmost faith in nature's provision for proper selection of nutriment by every human being. Yet we must not ignore the daily temptations to which the average child-bearing woman is exposed. Candy, ice-cream, cakes and pies, appealing though they be to the palate, so far as I can see have little value in the economy of the metabolism. The nutritional element most serviceable during pregnancy is protein. It not only replaces worn-out tissue, but contributes to the blood-forming mechanism. Of greatest importance is the fact that good protein blood levels prevent the onset of edema. It is no secret that the average American woman, left to her own dietary resources, tends to stress the carbohydrates and fats at the expense of the proteins.

The implication that an excessive gain in weight during pregnancy is of little significance is a challenge to accepted statistics. Waters has stated recently that women who have gained more than 23 pounds during their pregnancy show an incidence of toxemia of 4 per cent. This is about six times greater than the incidence among women who made a gain of less than 18 pounds. I should like to put this question: What company would issue a policy to a candidate for insurance if the applicant showed a gain of 30 or 40 pounds within a period of a few months? I am a strong believer in freedom whether it be freedom of thought, or of religion, or of food intake. Yet one does not have to go haywire in exercising this freedom. As medical advisers it is our duty to guide our patients

## THE EXPERIMENTAL PRODUCTION OF MENORRHAGIA BY ADMINISTRATION OF GONADOTROPINS\*†

E. G. HOLMSTROM, M.D., AND W. J. JONES, M.D., SALT LAKE CITY, UTAH

(From the Department of Obstetrics and Gynecology, University of Utah Medical School)

THE relationship of corpus luteum function to some cases of menorrhagia has interested investigators recently. Particularly Brewer and Jones<sup>1, 2</sup> and Holmstrom and McLennan<sup>3</sup> have reported studies of such cases. These investigators have tried to show that some cases of menorrhagia are associated with prolonged corpus luteum function. This is reflected in the endometrium by a failure of the secretory endometrium to be shed promptly and completely after onset of menstruation. Clinically this is manifested by prolonged bleeding. It has been assumed that, in such cases, there is continued production of progesterone during the bleeding phase of the cycle. In other words, there is failure of the corpus luteum to undergo complete regression prior to the onset of bleeding. To prove that such a situation exists is difficult due to the fact that we have no reliable test which will indicate that progesterone production is continuing beyond its normal limits. Determination of pregnanediol excretion in the urine has been found by numerous investigators to be, at best, a very rough index of corpus luteum function during the normal cycle. It is not a sufficiently sensitive test to allow its application to cases in which it is necessary to follow the variation in progesterone production from day to day.

In order to prove that the corpus luteum is functioning beyond the time that it ceases to function in the normal cycle, it has been necessary to examine the ovaries of patients during the episodes of prolonged bleeding. Not many cases have been studied to such an extent. A recent report by Brewer and Jones<sup>2</sup> is the most complete study of that sort which has been done and seems to justify the conclusion that such a corpus luteum-endometrium relationship does exist. Studies of corpora lutea removed during the bleeding phase of the cycle from women with menorrhagia showed the presence of lutein cells which were still apparently functioning.

This paper presents the results of some experimental studies which were carried out on normally menstruating women. We have tried to prolong the life of the corpus luteum without interfering with the length of the menstrual cycle. Endometrium was removed as necessary for complete study. Corpora lutea were also obtained for study in most cases.

\*Presented at the Sixteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Denver, Colorado, Sept. 23 to 25, 1948.

†Study was aided by a grant from the Schering Corporation, Bloomfield, New Jersey. The Luteotrophin was furnished by Squibb and Company. The chorionic gonadotropin (APL) and Premarin were furnished by Ayerst, McKenna & Harrison.

pleasing texture, and I do not see why a baby is not entitled to the same pleasure. Certainly a rubber nipple is a poor substitute in most respects for a woman's breast.

I wish that I had Dr. Luikhart's ability to control my patients' qualitative diet, as I am heartily in accord with him on the need for a high protein diet right through the entire pregnancy. But most of my patients will eat what they choose, and I do not have the forceful character to compel them to change their eating habits. I can urge them, but I can't compel them unless I wish to be the stern, punishing figure, which I find rather objectionable. So I have tried to allay their fears about any bad effects of diet.

The element of mortality which we heard discussed has been investigated more closely than in the past, and I think Dr. Reis very ably emphasized that in toxemia we get both the excessive weight gain and the tragic fetal accidents.

Actually the discussants and I are not so far apart. It is more a matter of technique in giving the woman the adequate diet that we all feel is essential, and at the same time not scaring her to death.



Fig. 1.



Fig. 2.



Fig. 3.

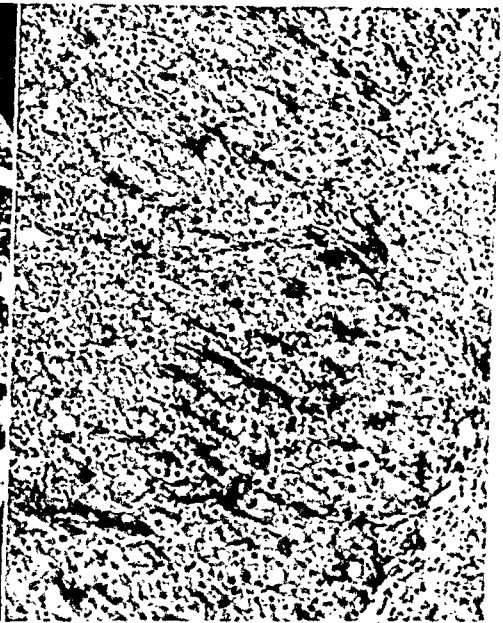


Fig. 4.

pseudopregnancy effect in the glands. Treatment was discontinued on day 39. Bleeding began two days later. Endometrium was obtained by curettage on day 5 of bleeding. The endometrium (Fig. 3) shows retention of the secretory glands and a picture generally characteristic of irregular shedding of the endometrium. The corpus luteum was also removed (Fig. 4). Although partly in regression, this shows some well-preserved lutein cells.

Previous reports indicate that it is possible to prolong the life of the corpus luteum artificially by the administration of either chorionic gonadotropin or luteotrophin. Brown and Bradbury<sup>4</sup> have shown that the life of the corpus luteum can be prolonged by the administration of chorionic gonadotropin during the postovulatory phase of the cycle. That this substance has little or no effect on the maturing follicles when given during the preovulatory phase was also demonstrated by the same authors. Browne and Venning<sup>5</sup> earlier showed that the postovulatory phase of the cycle could be extended up to seventeen days beyond the time of expected bleeding by the administration of chorionic gonadotropin. Prolongation of function of the corpus luteum by administration of this hormone does not, however, reproduce the situation as seen clinically because of the fact that the length of the cycle is interfered with. One of the chief characteristics of the condition known as irregular shedding of the endometrium is the fact that, although the bleeding phase of the cycle is prolonged, there is no change in the total cycle length. Therefore, it was decided to investigate the property of another gonadotropin, luteotrophin, to determine what its effect would be on the already developed corpus luteum. Astwood<sup>6</sup> demonstrated that corpus luteum function, as evidenced by progesterone secretion, cannot be activated by either the follicle-stimulating or luteinizing hormone, but requires a third pituitary gonadotropin, the luteotrophin factor. This is closely allied to, if not the same as, prolactin. Evans et al.<sup>7</sup> showed that the lactogenic hormone of the pituitary favored the production of placentomas in normal, adrenalectomized, and hypophysectomized animals but not in ovariectomized ones. These workers believed that the effect was due to a direct action of the hormone on the corpus luteum, for hypertrophic, well-preserved corpora lutea were demonstrated to be present. In addition to this, the follicles and interstitial tissues were markedly subnormal. This may indicate that the lactogenic hormone (luteotrophin) suppresses the formation of the follicle-stimulating hormone. Gaarenstroom and de Jongh<sup>8</sup> also believe that luteotrophin is required for the production of progesterone after the corpus luteum has been formed.

The following experiments, carried out on presumably normal women patients, will show that it is possible to prolong the functional stage of the corpus luteum by the administration of chorionic gonadotropin. This prolongation of the corpus luteum function is reflected in the endometrium by prolongation of the shedding phase. The effect of luteotrophin in this regard is questionable.

Because of space limitation it is not possible to present the details of all the experimental cases. Two cases will be presented to demonstrate the effects noted from the administration of the two hormones.

### Experimental Cases

CASE 1.—Aged 18 years, para 0, cycle 28 to 30 days.

Original endometrial biopsy (Fig. 1) shows early secretory changes in the glands corresponding to about the 18th day of the cycle. On day No. 25 of the cycle, chorionic gonadotropin (APL) administration was begun. Patient received 6,000 International Units daily from day 25 to day 39. Endometrial biopsy taken on day 37 (Fig. 2) shows marked

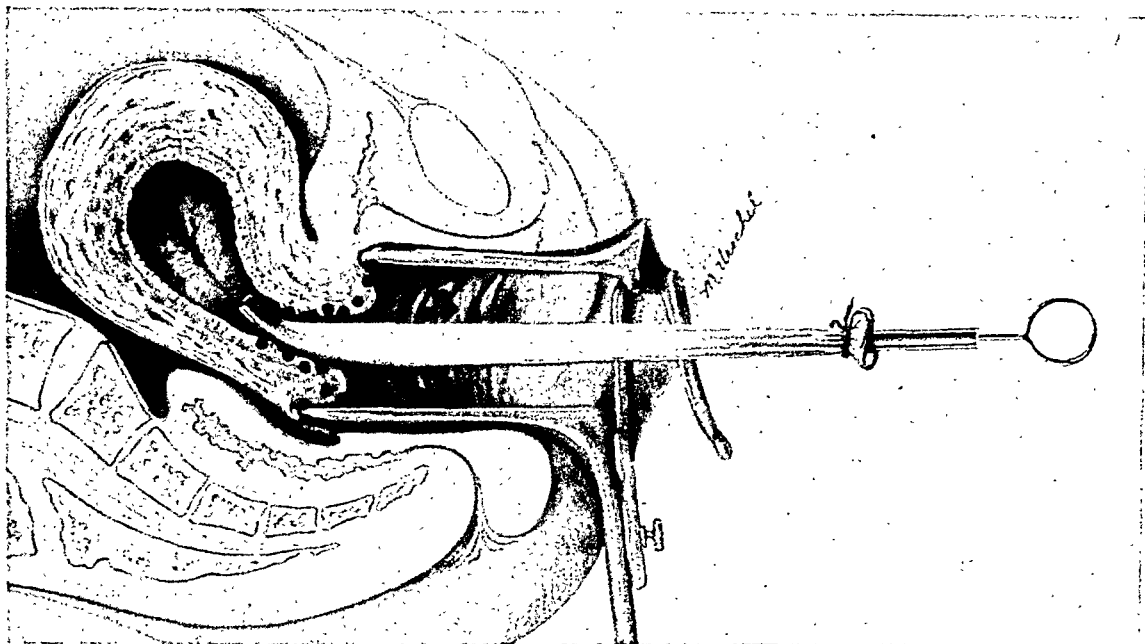


Fig. 2.—Diagrammatic cross section showing culture tube through cervix beyond the internal os. Finger cot has been drawn taut and the stylet partially inserted preparatory to perforating the stretched rubber protecting the end of the metal tube. Vaginal and cervical flora indicated by dots.

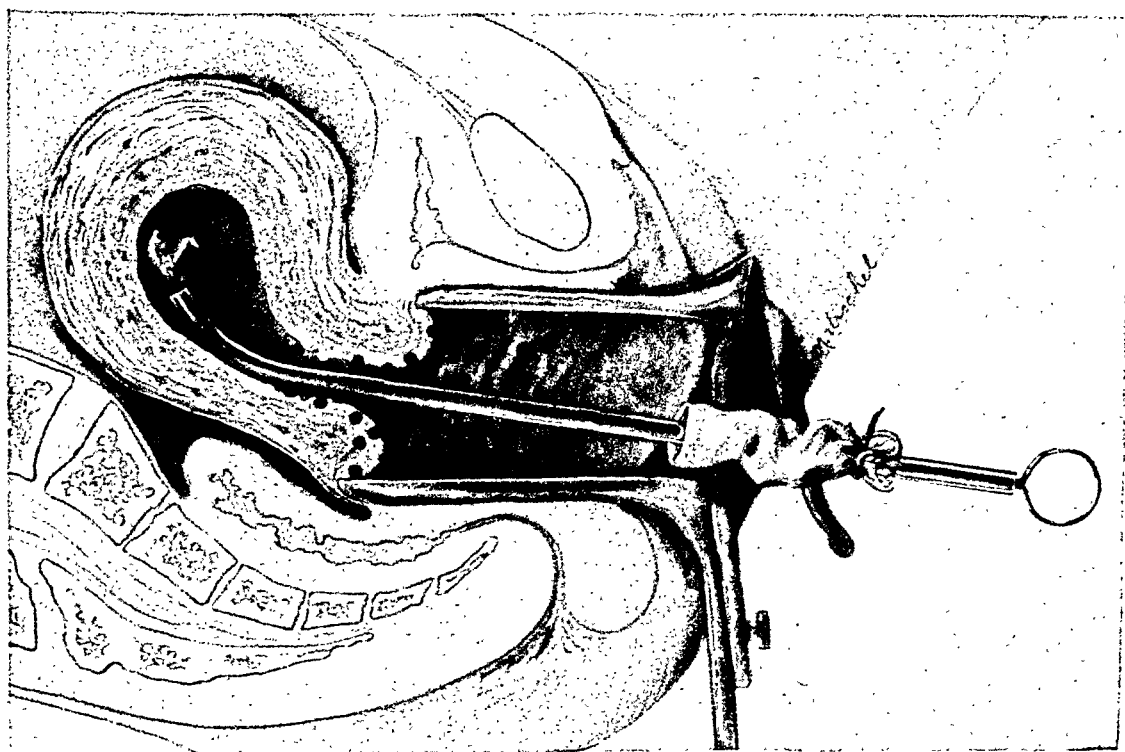


Fig. 3.—Diagrammatic cross section revealing wire loop in place following perforation and retraction of the finger cot which is shown retracted into the vagina. Contamination with vaginal and cervical flora is avoided and a culture representing the true uterine flora is thus obtained.



Fig. 5.

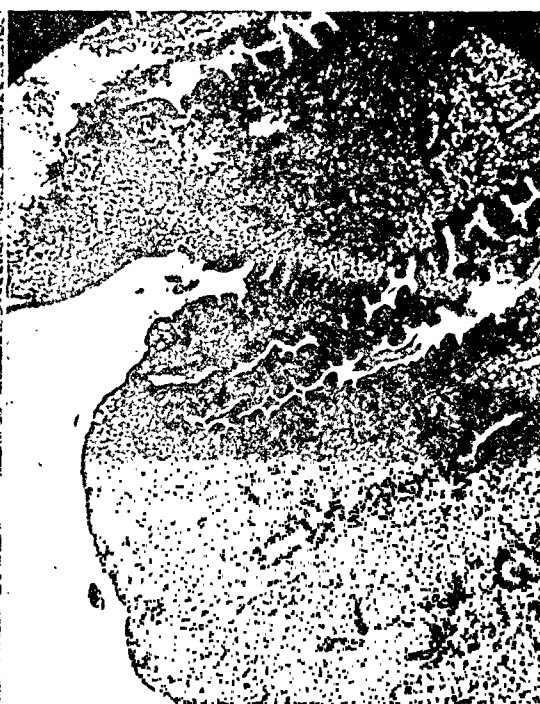


Fig. 6.

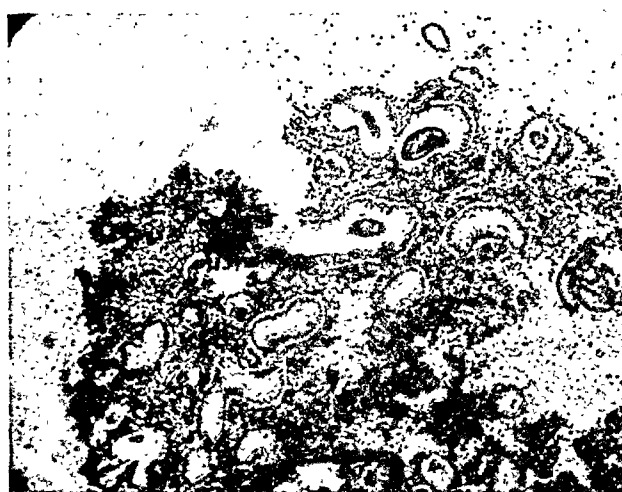


Fig. 7.

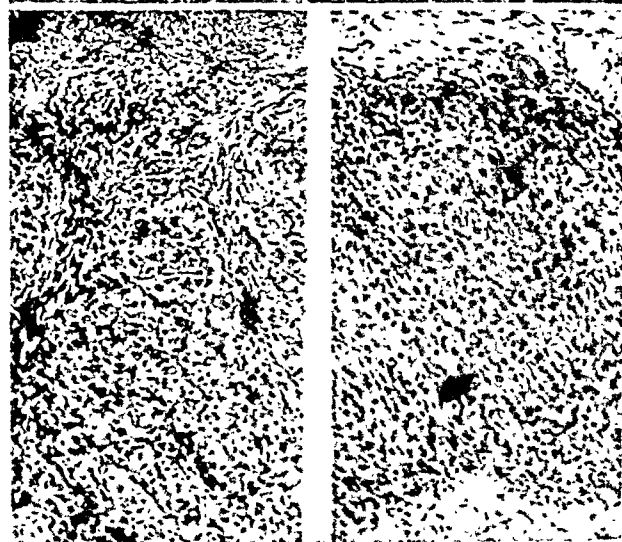


Fig. 8.

Fig. 9.



in turn, is reflected in the corpus luteum and finally in the end organ, the endometrium. We know that it is possible to cut down the period of bleeding in patients with irregular shedding of the endometrium by the administration of estrogen just prior to and during the bleeding phase. This is well exemplified in the following case:

CASE 3.—Aged 30 years, para ii.

*Complaint:* prolonged and profuse menses for the past seven years. Menstrual cycle regularly 30 to 34 days. Flow lasts up to ten days and is exceptionally profuse. Original dilatation and curettage were done on the fifth day of bleeding. Section of curettage material (Fig. 10) shows marked retention of secretory glands and typical picture of irregular shedding of the endometrium. *Treatment:* Premarin, 3.75 mg. daily, beginning four days prior to the expected menses, continuing during bleeding phase. *Result:* diminution in flow. Endometrial biopsy taken on fifth day of bleeding (Fig. 11) shows marked acceleration of the shedding and healing process with re-formation of the surface epithelium.

This case demonstrates the effect of estrogen on endometrial regeneration and growth. We have now had the opportunity to use oral estrogen, as described, in several cases of irregular shedding of the endometrium. We have had good results in cutting down the length of the bleeding phase when the administration is begun about four days prior to the expected bleeding and continued during the bleeding phase. Smith and Smith<sup>11</sup> have shown that progesterone inhibits the secretion of follicle-stimulating hormone of the pituitary and thus the elaboration of estrogen. One might, therefore, think of the hormonal relationships which are disturbed in cases of irregular shedding of the endometrium as depicted in Fig. 12.

### Summary and Conclusions

1. Luteotrophin, administered in daily dosage of 500 units after the corpus luteum has been formed, will not prolong the menstrual cycle but will cause the corpus luteum regression to be retarded.

2. It is postulated that some cases of menorrhagia, in which there is no local lesion in the uterus to explain the excessive bleeding, may be due to incomplete withdrawal of luteotrophin stimulation prior to the onset of bleeding.

3. Administration of estrogen just prior to and during the bleeding phase will decrease the duration of menstrual bleeding.

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### Discussion

DR. WILLARD M. ALLEN, St. Louis, Mo.—This paper has interested me a great deal since it provides some evidence regarding the life span of the corpus luteum and

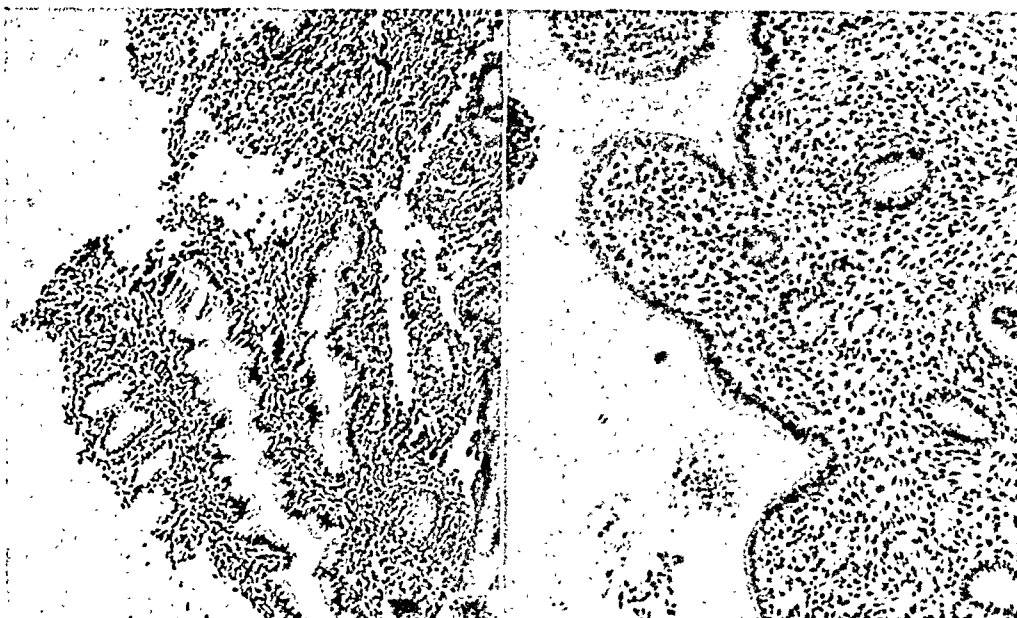
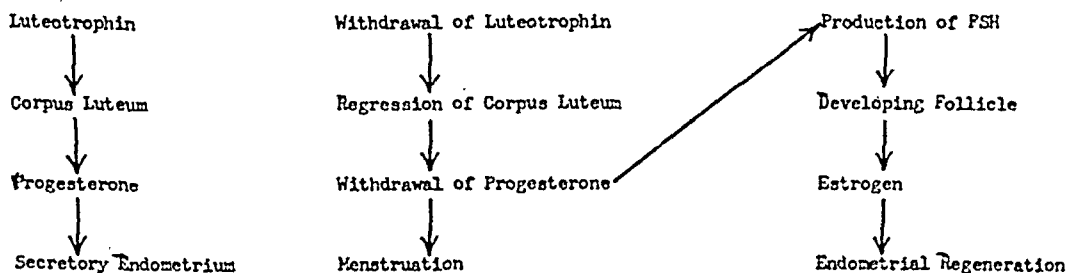


Fig. 10.

Fig. 11.

NORMAL CYCLE



IRREGULAR SHEDDING

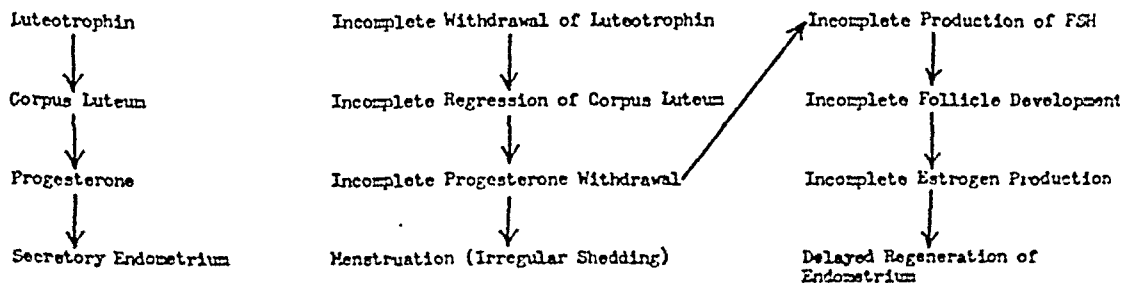


Fig. 12.

Also Brewer and Jones, and Holmstrom and McLennon have more recently reported on this group. This secretory type of menorrhagia has been divided into irregular ripening and irregular shedding. In the irregular ripening, parts of the endometrium do not develop into a full secretory endometrium while other areas do show a full secretory phase. In irregular shedding, the fully ripened endometrium does not come away from the uterus, the tortuous corkscrew glands being found after seven to ten days of continuous bleeding, whereas ordinarily all of the secretory glands have sloughed away by the third to fifth day of the normal cycle.

The present theory of the hormone sequence in the menstrual cycle includes the following:

The pituitary gland produces follicle-stimulating hormone which stimulates the growing follicle to develop, and if the pituitary also produces a small amount of luteinizing hormone the follicle will secrete estradiol. The increasing estradiol depresses the pituitary from producing too much F.S.H. but further stimulates the production of increasing L.H. The increasing L.H. produces ovulation and the formation of a corpus luteum, but the corpus luteum does not secrete progesterone until luteotrophin is secreted from the pituitary gland, which continues for two weeks and ceases followed by menstruation.

Doctors Holmstrom and Jones have worked out a fascinating experiment by introducing increased amounts of luteotrophin after a normal corpus luteum has been formed to test a logical theory that this may be a cause of menorrhagia. Apparently an increased stimulation of that normal corpus luteum did occur with prolonged lutein effect, irregular shedding of the endometrium, and menorrhagia. It is interesting that the pregnancy hormone (chorionic gonadotropin) delays menstruation (as one would expect for the benefit of pregnancy) and luteotrophin, the supposed true pituitary stimulator of function of the corpus luteum, does not delay menstruation. I wonder how the large amounts of chorionic gonadotropin (similar or identical to the luteinizing hormone, L.H.) produces pseudopregnancy, since that hormone supposedly does not cause the secretion of progesterone.

Drs. Holmstrom and Jones are to be congratulated on their original clinical experiment. While very few cases are necessary to reach a valid conclusion if they are carefully studied, the acceptance of the production of experimental menorrhagia by luteotrophin from the treatment of two patients for one cycle each needs confirmation. I am certain they will continue their studies and hope they will report further to this association next year.

While we can tell a certain amount about the function of the corpus luteum from looking at the gland microscopically, I doubt that one can say this gland shows more regression than another when the changes seem relatively slight as in these cases.

DR. HOLMSTROM (Closing).—I would like to refer to Fig. 12. This is a diagram of what we think happens in the menstrual cycle. I do not know whether it is correct or not. Here are shown the events in the normal cycle beginning with withdrawal of luteotrophin, withdrawal of progesterone, and then menstruation. Coincidental with the withdrawal of progesterone there is production of follicle-stimulating hormone which stimulates the follicle to produce estrogen. This, in turn, acts on the endometrium and results in healing. In the case of irregular shedding there is incomplete withdrawal of the luteotrophin, incomplete withdrawal of progesterone, and irregular healing. The incomplete production of follicle-stimulating hormone results in an incomplete estrogen production and delayed healing of the endometrium. I think that this can be picked apart but it is something to think about.

We are, of course, continuing the studies. As Dr. Gray pointed out, a few cases do not prove anything. It is difficult to get patients who are normal and in whom we can ultimately get the corpora lutea for study. Fortunately we have access to patients who are sent to us for sterilization. We try to keep these around the ward for a few months while carrying on the studies. This it is not always possible to do.

the factors which control it. The corpus luteum is a unique endocrine gland. Its life span is fixed at about two weeks, but, nevertheless, under the stimulus of pregnancy it survives in a functionally active state for variable periods of time depending on the species. This prolongation of activity during pregnancy is due to the specific effect of a gonadotrophic hormone elaborated by the placenta. The products of conception, in a sense, control their own destiny since the chorionic gonadotrophin stimulates the corpus luteum to produce progesterone and this in turn keeps the endometrium and myometrium in the proper state to permit implantation and growth of the embryo. A more intriguing question perhaps pertains to the nonpregnant state. Why does the corpus luteum regress after twelve to fourteen days if it does not receive the signal that there is an embryo in the uterus? Dr. Holmstrom's studies do not answer this question but they do show that the behavior of the corpus luteum can be altered in the nonpregnant woman by gonadotrophins, and, further, they show that bleeding can occur when the corpus luteum appears to be continuing to produce progesterone. This stimulation of the corpus luteum apparently leads to partial breakdown of the endometrium and gives the clinical and pathological picture of irregular shedding.

Breakdown and bleeding from the endometrium can be produced by two methods. The administration of estrogen followed by withdrawal of the hormone leads to bleeding, called estrogen-deprivation bleeding. Similarly, the administration of progesterone is followed by progesterone-withdrawal bleeding, provided the uterus is under the influence of estrogen. There is, however, another type of bleeding which can be induced. This bleeding occurs during treatment. For example, the continued administration of estrogen to a woman without functioning ovaries produces bleeding after a period of about six weeks. This "break-through" bleeding is associated with hyperplasia of the endometrium. The bleeding which Dr. Holmstrom describes seems to be a "break-through" type of bleeding but it would seem to be occurring in an endometrium showing the effects of prolonged stimulation by progesterone rather than estrogen. This can be called "progesterone break-through" bleeding.

Some studies which Dr. W. H. Masters and I have been making in aged women tend to confirm this idea that bleeding can occur from a progestational endometrium without withdrawal of progesterone. We have found that the uterus of postmenopausal woman can be completely rejuvenated by the use of proper quantities of estrogen and progesterone, and regular cycles can be induced. The important point is this, the administration of 10 mg. of progesterone daily for ten days produces, in a uterus which has been conditioned with estrogen, a fully developed progestational endometrium. Bleeding and shedding of the endometrium occur normally after discontinuing the progesterone. However, if the progesterone is continued at this same level of dosage for another ten days, i.e., twenty days in all, bleeding has begun in some of the cases before the progesterone has been discontinued. This progesterone break-through bleeding occurs in the presence of a progestational endometrium. With smaller doses of progesterone break-through bleeding begins even earlier. The findings are in agreement with those reported by Dr. Holmstrom. Both studies suggest that abnormal involution of the corpus luteum can be expected to produce abnormal uterine bleeding.

DR. LAMAN A. GRAY, Louisville, Ky.—Of cases of functional uterine bleeding supposedly caused by hormone dyscrasias, approximately 80 per cent are associated with non-secretory endometrium, with presumed absent ovulation and corpus luteum formation. Approximately 20 per cent of cases show a secretory endometrium, and must indicate the presence of a corpus luteum. Most cases of functional bleeding associated with secretory endometrium occur clinically as menorrhagia, or prolonged, often profuse, but relatively regular, menstrual flow. This is in contradistinction to the anovulatory type, most often associated with irregular bleeding or metrorrhagia.

The 20 per cent with secretory endometrium have been divided and classified in this country particularly by two sets of investigators, Traut and his co-workers, and McKelvey.

## SAPHENOUS PHLEBECTOMY FOR VARICOSE VEINS DURING PREGNANCY\*

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LAFAYETTE, IND.

(From the Departments of Surgery and Obstetrics and Gynecology, St. Elizabeth Hospital)

THE purpose of this paper is to discuss the current status of radical care of varicose veins in pregnancy and to present a study of twenty cases in which saphenous phlebectomy was done during the course of pregnancy.

In 1579, Ambrose Paré<sup>1</sup> wrote that it is best not to meddle with varicose veins during pregnancy. Current textbooks adhere to conservatism or deprecate ligation, but offer no valid reason for this contention. McPheeters<sup>2</sup> states that simple ligation of varices during pregnancy has been a 100 per cent failure and is not recommended. Allen<sup>3</sup> and Wright<sup>4</sup> in their recent volumes on vascular diseases practically fail to consider the pregnant woman, and neither offers specific advice. Linton<sup>5</sup> writes that he would rather defer radical venous surgery until after the pregnancy.

The authors had been dissatisfied with the results which they frequently observed from such methods as bandaging and expectant rest. Simple ligation and/or injection per se have not proved to be definitive therapy. Recognizing the recent advances which have been made in vascular surgery, and believing that complete eradication of the incompetent saphenous system, or the incompetent portions of it, would be a desirable goal, we began two years ago to treat patients by segmental saphenous phlebectomy during pregnancy for the more severe cases of pre-existing varicosities.

Since beginning this paper the authors have found that others are using a similar procedure. Shank,<sup>6</sup> during the past six months, reports a series of patients treated in the authors' fashion and he<sup>7</sup> is enthusiastically continuing to favor the method. He has obtained uniformly good results from radical operation followed by injection of the residual varices. Ochsner personally communicated with Shank and stated that this is the treatment carried out in his clinic. Mullane<sup>8</sup> has recently begun some ligating of the saphenous vein and stripping it to the ankle. De Takats<sup>9</sup> states that his former recommendation in Curtis' *A Textbook of Gynecology* holds, and now<sup>10</sup> even stripping of the veins is done up to the seventh month of pregnancy.

### Rationale

The recognition and treatment of dilated, prominent, or varicose veins necessitates a good understanding of the factors affecting venous pressure. It is not necessary at this time to review the entire subject of venous circulation and abnormalities of it, but merely to emphasize the mechanism of venous stasis in the lower extremity plus the effect of pregnancy.

\*Presented at the Sixteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Denver, Colorado, Sept. 23 to 25, 1948.

### Postscript

Administration of Luteotrophin to subsequent patients has failed to result in clinical menorrhagia or in the endometrial changes characteristic of irregular shedding of the endometrium. The effect on the corpus luteum was again noted as described above. This will be further discussed in a later paper.

of a certain amount of confusion with regard to the details, is generally accepted as the best form of therapy today. Thus, the pregnant woman with pre-existing varicose veins is entitled to phlebectomy at the highest level and any lower levels at which backflow filling from the deep system may be demonstrable.

### Evaluation of Venous Stasis

Venous stasis evaluation consists of the proper interpretation of its manifestations. Of these, the principal subjective manifestations are pain, swelling, a sense of fullness or heaviness, and last but not least, fatigability. The objective findings are visible or palpable, dilated, superficial veins, usually tortuous, throughout the distribution of the saphenous system. The proximal portion of the saphenous trunk may or may not be visible or palpable, contingent upon the degree and duration of the incompetency. Localized bulging in the wall of the saphenous or its tributaries usually represents blowout formation at the level of an incompetent, perforating tributary.

Examination of these patients should include one or more of the accepted tests for incompetency, such as the Trendelenburg, multiple tourniquets, double ace bandage, and Perthe's test.

Patency of the deep system is determined by the time-honored method of semi-elastic bandage compression of the extremity and the patient walking vigorously for a specific period of time. If the symptoms are relieved, a good result may be anticipated from phlebectomy, but aggravation of the symptoms warrants reconsideration.

A reliable procedure, and one most commonly employed by the authors, is Homans'<sup>17</sup> modification of the Schwartz test, i.e., if the valves of the internal saphenous vein are incompetent, fingers placed over the proximal portion of it feel the impulse when the saphenous trunk or varicosities below are snapped with a finger of the other hand.

Adams<sup>14</sup> describes a test as follows: "If the finger of the palpating hand of the examiner be placed over the saphenous opening of the patient in the standing position, back flow in the incompetent cases is readily detected as a palpable venous thrill when the patient coughs or strains." He believes that saphenous interruption is indicated in all cases where his test is positive.

It must be remembered that during pregnancy all subjective and objective manifestations are accentuated and should be evaluated accordingly. No two cases are alike and each must be individualized. High phlebectomy may be done with assurance of improvement in all cases, but it is better to defer interruption at lower levels if their competency is in doubt.

It is assumed that other peripheral vascular diseases have been differentiated, such as dilatation of the veins due to a proximal arteriovenous fistula, deep venous insufficiency, and reflux through the hypogastric tributaries. The pattern of the latter is distinctive in the gluteal and vulvar areas and not readily confused with the saphenous distribution; however, dilatation of superficial obturator tributaries may be mistaken for those of the saphenous high in the thigh.

The authors submit the following criteria for saphenous segmental phlebectomy in pregnancy:

1. Pre-existing varicose veins.
2. Presence of one or more subjective manifestations.
3. Demonstration of incompetence of the saphenous system by one or more of the accepted tests.
4. The advent of superficial thrombophlebitis.
5. Request by the patient for riddance and relief.

The pathogenesis of varicose veins involves consideration of hydrostatic pressure. We are concerned with both the femoral or deep, and the saphenous or superficial systems. The latter is of primary interest in the subject at hand but the femoral system is intimately involved through the well-known connections at various levels. Thus, Pascal's Law applies, that pressure exerted upon an enclosed fluid is transmitted undiminished in all directions and acts with equal intensity on all surfaces. Delbet<sup>11</sup> in 1902, and later Murphy and Mengert,<sup>12</sup> demonstrated the effect of increased intra-abdominal tension with proportionate increases in venous pressure in the leg. McPheeters<sup>13</sup> showed that pressure increases toward the ankle because of gravity.

Adams<sup>14</sup> in 1939 made an important contribution to the complete understanding of the cause and surgical treatment of varicose veins by differentiating between pure gravity effect and that of voluntary muscular effort, such as coughing or straining. He found, as others did, that standing pressures in the saphenous system before and after high interruption were identical; however, after interruption, the significant alteration is a decrease in straining pressure. It is to be remembered that hydrostatic pressure is transmitted through the communicating veins between the superficial and deep systems, unless the two systems are disconnected by interruption at the affected levels.

Both Burwell<sup>15</sup> and Veal<sup>16</sup> reported comparative studies of the venous pressure in the upper and lower limbs as it changes during the course of pregnancy, and recognized another effect on hydrostatic pressure, this being the enlarging uterus and the resistance it offers to venous return. Occlusion of the large abdominal and pelvic veins by actual compression and increased intra-abdominal tension in pregnancy increases venous pressure in the lower limb. The effect of the placenta is that of a modified arteriovenous fistula and is an additional factor.

A competent and strong saphenous system may become relatively incompetent and dilated during pregnancy because of its normal elasticity, but obviously it recovers completely in most women. Failure to recover results in permanent varicosities and concomitant venous stasis of some degree. Inherent connective tissue deficiency, hormonal changes, anatomical variations, defective valves, and occupation are some of the factors interfering with recovery.

To summarize the status of the venous circulation of the lower extremity with varicose veins during pregnancy we quote from Adams'<sup>14</sup> hypothesis: "With a patient standing so that the saphenous system is distended with blood, an increase in pressure exerted on any portion of this system is transmitted equally throughout the system. This is modified by the presence of an overflow sump which is the right side of the heart, and so the standing pressure is the gravity effect of the column of blood above it. This head of blood, peculiar to man, because of his erect posture, is the most important factor in the causation of varicose veins. . . . Increased intra-abdominal pressure interrupts by compression the column of blood in its intra-abdominal course and our sump is disconnected. We are then dealing with a closed system which obeys Pascal's Law. Pressure and not reversal of flow is the dilating factor. Reversal of flow, however, does permit constant filling of an elastic system so that the full effects of intra-abdominal increases in pressure may be transmitted according to Pascal's Law. Man, again because of coordinated muscular acts peculiar to him because of his erect posture, is subject to unusual increases in intra-abdominal pressures."

Certainly pregnancy and the process of parturition contribute to the causation and aggravation of varicose veins in the vulnerable individual. Therefore, surgical measures directed toward the reduction of straining pressure in the saphenous system are indicated. Surgical management of varicose veins, in spite



and vulvar varicosities are considered problems in pregnancy, and might be expected to exist with varicosities of the extremities, their coexistence in the series was but 20 per cent.

Only the legs were involved in four patients, whereas the thigh alone was affected in one. Fifty per cent were bilateral. Of the unilateral, five were left and four were right. Two were exhibiting evidence of thrombophlebitis and this finding prompted early surgical intervention.

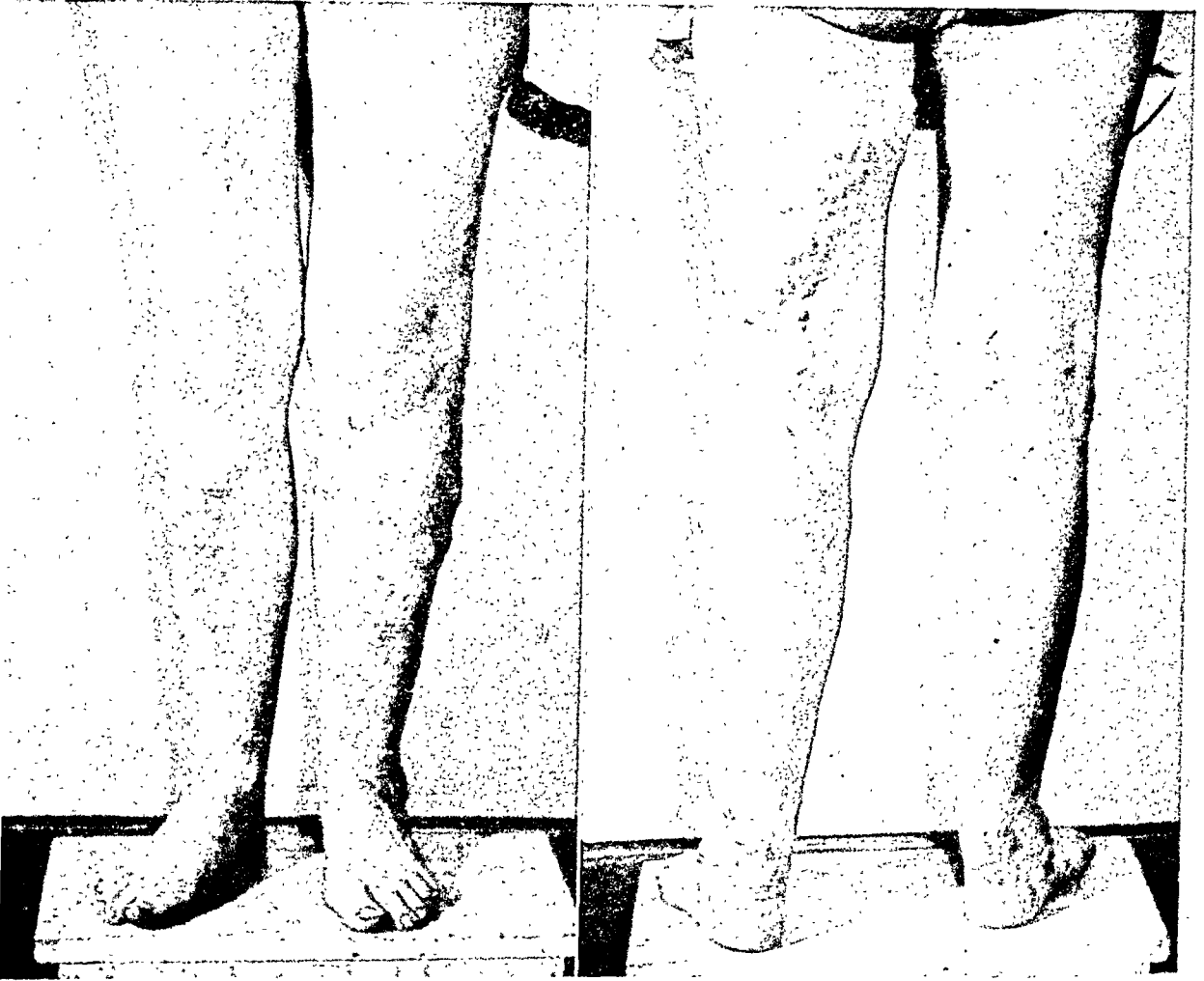


Fig. 1.—Twenty-four-year-old gravida iii with varicosities of four years' duration, just prior to phlebectomy at thirtieth week.

The operative procedure as described was done on patients varying from the tenth week to the thirtieth week of pregnancy, the average being twenty-two weeks. Request by the patient for riddance and relief rather than proposal of the authors instigated phlebectomy except in the two complicated cases, where it was recommended.

All of the cases had high phlebectomy and one-half were bilateral. Lower level phlebectomy also was done in all but three cases. It is interesting that only one-half the series required more than one stage to complete the surgery.

Transient false labor ensued in two patients nearest term, subsiding under sedation and rest. The average stay in the hospital for each stage was nineteen

In view of the known potential hazards in connection with any treatment of varicosities, the authors emphasize the utmost care in the selection of patients to be treated by this approach until sufficient evidence is accumulated further to justify its use.

### Operative Procedure

Ligation, phlebectomy, and interruption are terms used rather loosely in current literature. In this study, segmental phlebectomy was done and consists of the removal of a segment of the vein, both at the saphenofemoral junction and lower levels in the superficial system.

The patient is hospitalized, preferably on the day prior to surgery. The office is no place to do this work. Simple ligation is deprecated. The various tests are repeated and the saphenous trunk or blow-outs in it are marked with 15 per cent silver nitrate or a reliable dye. Preoperative sedation is given in the form of morphine sulfate,  $\frac{1}{4}$  grain and scopolamine,  $\frac{1}{150}$  grain. The operative area is prepared and draped and local anesthesia is used throughout.

The incision should be about 2 inches long and placed just medial to the line of the femoral artery which is identified by palpation. A nearly vertical incision, beginning at the inguinal fold, is preferable to one parallel with it, for it allows better exposure and anticipates any difficulty arising from an unusually low position of the fossa ovalis and the common tributaries. The saphenous vein is identified and divided between clamps at the lower angle of the wound. The proximal portion is cleared by blunt dissection and individual ligation of each tributary as encountered until the saphenofemoral junction is demonstrated. The trunk is ligated with chromic 0 catgut flush with the femoral vein and a suture placed just distal to the initial ligature. The isolated segment of the vein is then removed. The superficial fascia is approximated with continuous chromic 00 catgut and the skin with dermal mattress sutures.

The previously marked lower portions or blowouts of the saphenous vein or its tributaries are demonstrated through longitudinal incisions. Tributaries of the segment to be resected, especially those of the perforating type, are divided and ligated. The proximal and distal ends of the saphenous or its major tributaries are also ligated. Segments are commonly removed by avulsion when it is feasible because of the proximity of lower level approaches. Sterile dressings are applied. Ace bandage compression is used if lower level segments have been resected and is optional during the subsequent weeks. Activity is encouraged while in the hospital and following dismissal, which is usually on the day of operation. The patient is seen and sutures removed within one week. Persistent residual varices are injected in the office. The patients are followed for one year and through any future pregnancy.

### Analysis of Cases

From 700 pregnancies, 20 patients were selected in accordance with the foregoing criteria and were treated by phlebectomy. The average age for the series was 30 years, the youngest being 19 and the oldest 37. Three were pregnant for the first time, 3 the second, 9 the third, and 5 had had more than three pregnancies. Among the 17 multiparas, the first pregnancy occurred from 2 to 20 years prior to treatment. Seven years was the average age of the oldest child.

The symptoms were as follows: fifteen, or 75 per cent, complained of pain, fourteen of swelling, twelve of aching, ten of fatigue, and four of a sense of fullness. Only one had all the above symptoms, while one had none of them, but the latter complained of large veins. Inadequate obliterative treatment prior to pregnancy had been done elsewhere in four patients. Although hemorrhoids

During this same period the authors encountered an instance of postpartum superficial thrombophlebitis in pre-existing varicosities, and one of first-trimester iliofemoral phlebothrombosis,<sup>18</sup> both of which had successful surgical intervention. These cases, though relevant, are not included in this study.

### Conclusions

Individualized radical surgical measures for pre-existing varicose veins offer an opportunity for therapy in the pregnant woman at the time when it is needed most. It can be accomplished without any greater hazard than in the nonpregnant. In the opinion of the authors, the results obtained, the satisfaction of the patient, and the absence of thromboembolic disease justify continued consideration of saphenous phlebectomy during pregnancy. By closer collaboration with surgeons trained in the treatment of vascular disorders, obstetricians can improve the care of their patients with varicosities.

Acknowledgment is made to Drs. Ira Cole, H. E. Klepinger, and Catherine Balkema for their permission to use cases in this study.

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### Discussion

DR. CONRAD G. COLLINS, New Orleans, La.—The marked lowering of maternal mortality caused by sepsis, toxemia, and, to some extent, hemorrhage, evident in the past fifteen years has brought to light other conditions which are just as lethal, though not as frequent. These latter factors were so completely overshadowed by the major triad, sepsis, toxemia, and hemorrhage that they received little or no attention. A review of any recent large series of cases, either gynecologic or obstetric, shows that anywhere from 10 per cent to 20 per cent of the deaths are due to pulmonary embolism. It is well established that varicosities are one of the more important etiological factors in the production of intravascular clotting. The ideas propounded and the results expressed in the paper by Drs. Peyton and Loop that we have just heard, are so basically sound that we should completely revise our concepts as to the management of varicose veins in the pregnant woman. An active surgical attack on this pathological process will mean not only a more comfortable patient, physically and mentally, but also a prophylactic measure against phlebothrombosis, thrombophlebitis, and pulmonary embolism.

hours. There was immediate relief from pain and aching in all cases. A grateful absence of fatigue was noticed within a few days by those so afflicted. Except for one case of persistent ankle edema, which continued until delivery, the swelling and sense of fullness disappeared within two weeks in all patients, including a few women who experienced a temporary increase in swelling. A bothersome vulvar edema of two weeks' duration appeared in one patient.

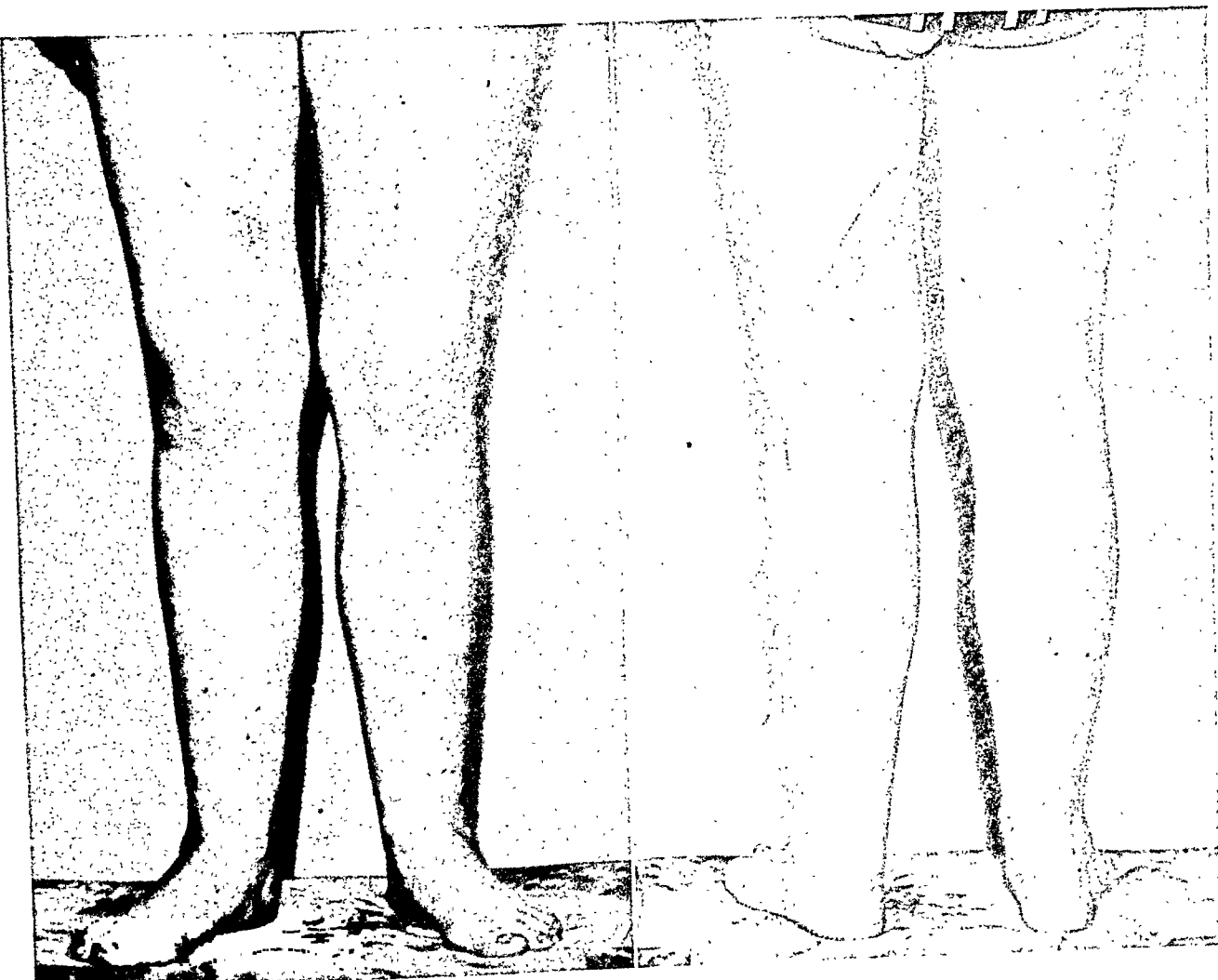


Fig. 2.—Same patient nine months post partum. The results are definitive.

Each patient went to full term and was delivered of a normal infant. One patient with two previous cesareans was sectioned. One primigravida had a prolonged labor with an occiput posterior position. The multiparas averaged four and one-half hours of labor. Continuation of relief and the absence of any vascular complication were noted in the postpartum period. Early ambulation was the rule.

For periods ranging from three months to two years since delivery, satisfactory results prevail. Certain local sequelae such as painful or hypertrophic scars and parasthesia occurred in four patients. Latent undesirable effects were limited to two cases in which aching discomfort in the lower limbs developed, with one complaining of this only during relative inactivity. Residual small varices were injected at six weeks or later in 50 per cent of the patients. One patient in this series is now being followed through her second pregnancy.

## SWEAT GLAND TUMORS OF THE VULVA\*

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MANY kinds of new growths may be found on the vulva. The variety of tissues found in its structure provides the possibility of a number of types of neoplastic activity. Displaced mammary tissue in the vulva, as observed by Mengert<sup>11</sup> and by Purvess and Hadley,<sup>8</sup> adds to these possibilities. The tumor which is of greatest clinical interest is carcinoma of the vulva which is almost invariably epidermoid in character. Adenocarcinoma, apart from tumors originating in Bartholin's gland, is occasionally, although very infrequently seen. If carcinoma of the vulva is the most spectacular of the neoplasms which occur in this area, the lesion which I am about to discuss may be placed among those which are clinically the least colorful of all. However, from the pathological point of view, they are most interesting and are deserving of greater consideration than they have received.

Hidradenoma is a tumor which arises from the sweat glands. Sweat glands, as glands in general, are divided by Maximoff<sup>15</sup> into three groups. The merocrine gland forms its secretion without damage to the cells of the gland, the secretion being extruded through ducts, leaving the cells of the gland intact. Holocrine glands form their secretion by the extrusion of the entire cytoplasm of the glandular cell, new cells being formed in order that the gland may continue to function. The apocrine gland occupies a position midway between these two. In the apocrine gland a portion of the cytoplasm bulges up over the level of the interior of the gland. The protruding portion is pinched off and becomes a part of the secretion of the gland. Homma<sup>4</sup> suggests a more simple classification of these glands, dividing them into two groups, the exocrine and the apocrine glands. Various observers who have studied these glands believe that there are gradations between the different groups and that all of them do not belong with entire definiteness to one or another group.

While these tumors may arise from sweat glands of any type, it is from those of the apocrine variety that they most frequently originate. Apocrine glands are found widely in nature. In the lower animals they are plentifully present and are said by some authors to play a part in sex attraction. They are less frequently found in apes than in many animals of the frankly four-footed groups. Such glands have been identified in the skin of the larger apes, especially in the gorilla. They are, according to Homma,<sup>4</sup> three times as plentiful in the Negro as in the white man. In man they are found especially in the axilla, in the perianal region, in the groins and about the nipple and on the vulva. They do not develop until puberty.

\*Presented at the Sixteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Denver, Colorado, Sept. 23 to 25, 1918.

The authors have rightly emphasized that before surgical therapy is applied two criteria should be met: First, it should be definitely established that the veins are varicose in type and not simply prominent normally functioning venous channels. Second, that should true varicosities exist, the competency of the deep venous system should be firmly established.

Up until the past year, upon the advice of the surgical division at Tulane, we managed cases of varicose veins complicating pregnancy by means of compression bandages applied antepartal, intrapartal, and postpartal, abetted by early ambulation. Despite these measures a fair percentage of patients developed intravascular clotting in the varices, some antepartal and some postpartal. In addition they all have the complaints enumerated. During the past year, all patients with varicosities complicating pregnancy have been treated by antepartal active surgical therapy and the results parallel these described. The poor results reported in previous years in this condition were undoubtedly due to the lack of a full appreciation of the part played by the communicating veins in the re-establishment of varicosities. High-low ligation of, and stripping of, the long saphenous vein, or high-low ligation of the long saphenous with segmental phlebectomy seems to be the rational method of approach in the management of varicose veins complicating pregnancy.

DR. HAMILTON, Kansas City, Kan.—We have interested ourselves in this topic with the active cooperation of an excellent vascular surgeon, having followed this type of case since 1938 and accumulated 591 cases in so doing. During this time, our multigravidas have outnumbered our primigravidas three to one. Our age limits have been a bit wider than have been mentioned before. The treatment has been of two types, being either ligation with injection or injection alone. We have actively treated not only the varicosities of the extremities but also those of the labia. It is interesting to note that none of the primigravidas showed any labial varicosities of great enough significance to cause us to institute therapy.

In our type of therapy, ligations in the labial varicosities have not run as high as they have run in our extremity therapy. In the ligation, we ligated and then did retrograde injection. We had unsatisfactory results in 4 per cent. On this 4 per cent I think we would have an improvement now because we are more free with our ligation than we were before, and most of our unsatisfactory results were a result of poor choice of techniques, rather than fault of method. As far as the recurrence figures are concerned, I regard them as being completely unreliable because I am quite certain that it would have been worse than appears, if we had been able to follow them up as far as we would like to. The significant and important thing is that not one patient aborted from therapy, and there was no embolism following therapy.

We were not as much interested in treating symptoms in the patient as we were in treating a disease entity. Our feeling was that one of the commonest causes of postpartum phlebothrombosis and thrombophlebitis is incompetent venous circulation in the lower extremity. So, we were interested, therefore, in treating any patient who shows an incompetent circulation.

In the course of this series, not one of these 591 cases, and I might add there were 450 or 500 others that are not included because the data on them was not sufficient for analysis, not one of these women experienced postpartum phlebothrombosis or thrombophlebitis.

DR. PEYTON (Closing).—We went very slowly in this study. We could have had probably three times as many cases, but we held the number down to rigid indications until we could get more evidence of the procedure's value. I hope that this report will provoke some publications because I found little or nothing on the subject. Another point is the use of the term ligation. As I said, when one says ligation, he means tying off the vein rather than doing a phlebectomy and getting tributaries as Dr. Collins emphasized. Phlebectomy is the only thing to do. Dr. Collins just said it should be emphasized that the surgeon who is to do this work should be trained in vascular diseases and disorders in order to get the results that the patient should have.

Fig. 1.

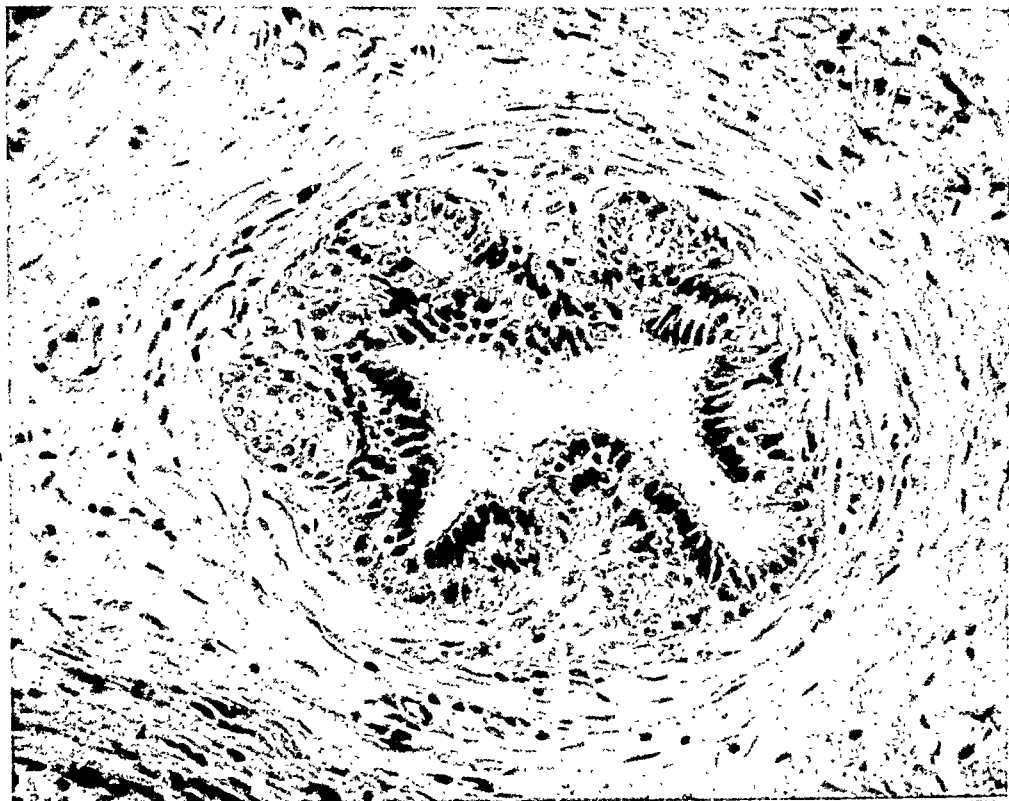


Fig. 2.

Fig. 1.—Apocrine sweat gland. The epithelium in two layers which is typical of this gland is clearly seen. ( $\times 300$ )

Fig. 2.—Apocrine sweat glands and sebaceous glands are frequently found together. The multiple layers of the epithelium of the sweat glands are shown. ( $\times 200$ )

Sweat gland tumors of the vulva were first accurately described in 1904 by Pick<sup>1</sup> who recognized the fact that they usually arise from the apocrine glands of the vulva. He believed that they arose from rudimentary glands, rather than from those which are fully developed. It is impossible to estimate their frequency since because of their small size and the fact that many of them produce no symptoms they are frequently overlooked. Labhardt<sup>7</sup> states that up to 1916 only eight cases had been reported and Cunningham and Hardy<sup>16</sup> state that up to 1947, 80 cases had appeared in print. Grossly, they are small, from 1 to 2 cm. in diameter and may be raised slightly above the surrounding surface of the skin. They cause no pain nor indeed any discomfort unless traumatized or unless infection occurs. In the latter case ulceration of the surface may take place and a discharge may be seen of a brown pulpy material. Many of those which have been reported have been excised incidentally at the time some form of vaginal operation was being done. In most instances the tumor may cause so little disturbance that the patient may carry it indefinitely. Most of them occur in the fifth decade. They are most often found on the labium majus but two cases appear in the literature in which the tumor was located upon the labium minus, that of Schickele,<sup>10</sup> and one of the cases of Novak.<sup>12</sup> One of the tumors here reported was found on the labium minus. In this case adenocarcinoma developed. Sebaceous glands, which are quite closely related to apocrine glands, are present on the labium minus. A somewhat similar sweat gland tumor, known as a spiradenoma, has been described as occurring on the scalp. It is interesting, in view of the much greater frequency with which these glands are found in Negroes, that none of the reported cases of hidradenoma was found in a Negro. All of the tumors here reported were found in white patients.

Microscopically apocrine glands are small acinar structures which are lined by a characteristic type of epithelium which is also typical of the tumors which arise from them. The cells of the epithelium is in many places stratified. Two or more layers may be found. This multiple-layered epithelium was described by Pick<sup>1</sup> and the fact that it is a characteristic of the gland from which these tumors arise must be borne in mind when forming an opinion as to the malignancy or the benignity of the tumor. The morphological characteristics of many of the tumors agree so strikingly with those of the apocrine type of sweat gland that Pick<sup>1</sup> rejected the idea, advanced by Schickele,<sup>10</sup> that they arise from remnants of the mesonephric duct. Pick describes a thin layer of myoepithelial cells which may be found between the epithelium and the *membrana propria*. These cells are found in a number of the tumors in this series. This myoepithelial layer, which is not everywhere present, may be found about the gland and its ductules. In some places, when the myoepithelial layer is present in a tumor, the epithelial cells may be placed directly upon the myoepithelial cells so that the multiplication of layers in such an area may be rather a pseudo-stratification than a real one. Myoepithelial cells are also found in the alveoli and particularly in the secretory ducts of the mammary gland. As the sweat glands and the mammary gland are associated morphogenetically this is not surprising. It is probable that the cells are contractile and that they aid in emptying the gland of its secretion. Myoepithelial cells are also found in the excretory duct of the lacrimal gland.

It was suggested by Pick that these tumors might be divided into two groups, the hidradenoma tubulare, which is supposed to develop from a fully developed gland, and the adenoma hidradenoides tubulare, which develops from a rudimentary gland. It is probable that both groups are developed from rudimentary glands and the term hidradenoma seems a sufficient designation for all tumors of this group.



Fig. 5.

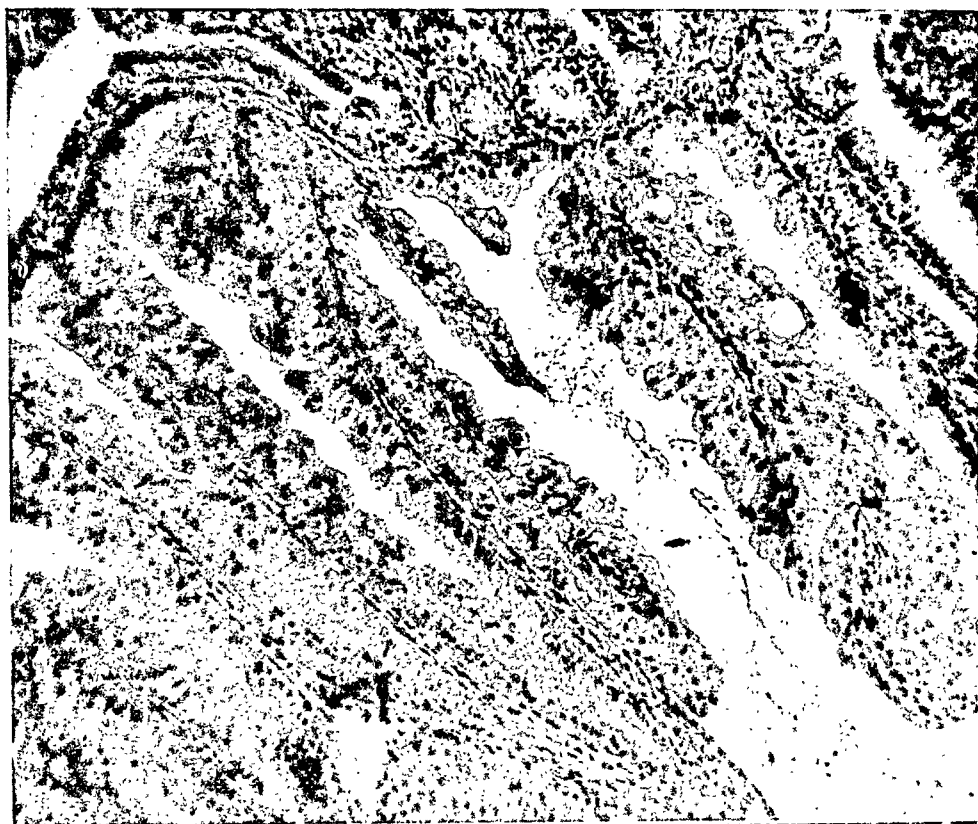


Fig. 6.

Fig. 5.—The tendency to papillary formation is shown. The typical epithelium in two layers is present. Basement membrane everywhere intact. Case of Dr. McNamara. ( $\times 300$ )

Fig. 6.—Sebaceous gland included within a hidradenoma. The tumor does not derive from the sebaceous gland. Two-layered epithelium may be seen. Case by Dr. W. C. Danforth. ( $\times 150$ )

Fig. 3.



Fig. 4.

Fig. 3.—Typical picture of hidradenoma. Moderate cystic dilatation in some spaces. Case of Dr. W. C. Danforth. (X100)

Fig. 4.—Typical papillary projections into the gland spaces. In several places in the wall of glandular spaces a two-layered epithelium is seen. The basement membrane is nowhere penetrated. Case of Dr. Augusta Webster. (X300)

I have been fortunate in being able to obtain slides of six of these tumors. Three occurred in our own hospital, one was obtained through the courtesy of Dr. Augusta Webster of the Passavant Hospital, one from Dr. W. L. MacNamara of the Veterans' Administration Hospital at Hines, Illinois, and another through the courtesy of Dr. H. C. Taylor, Jr. of Columbia University. The ages of four of these patients ranged from 42 to 73 years. The ages of the other two could not be ascertained.

The tumor consists of a knot of irregularly grouped gland ducts. In some of these growths papillary projections are seen extending into the gland spaces. While all of these tumors do not spring from glands of the apocrine type, the multiple-layered epithelium characteristic of this variety of gland is found in many of them. In those tumors in which papillary extensions into gland spaces are found, as in two of the cases in this group, the epithelium covering the extension may be in more than one layer. The upper layer may be of columnar cells of moderate height while the lower layer is made up of cells of cuboidal shape. In some glandular spaces a number of layers may be seen. Toward the ends of some of the gland spaces there may appear to be a solid mass of cells but this is often the result of the plane in which the section is cut. The basement membrane is everywhere intact and in the papillary projections, as in the other parts of the tumor, the staining reaction and the cellular morphology of malignancy are absent. In some of these tumors cystic dilatation of a part of the glandular spaces may be seen. Pick refers to them as tubulocystic adenomas.

In the paper of McDonald, Lovelady, and Waugh,<sup>14</sup> the tumor was described as malignant. The opinion as to its malignancy was based upon the fact that a multilayered epithelium was found and that papillary projections are frequently seen. Pick, in his paper in 1904, stated that the tumor resembled histologically an adenoma malignum but that a consideration of the double-layered epithelium of the gland from which it is derived, and which is reproduced in the tumor, should do away with any fear of its malignancy. In the paper referred to above the malignancy was described as of low grade and it was stated that no metastases were seen. No recurrences were noted and simple excision was the recommended treatment. Our experience causes us rather to agree with Aschheim,<sup>17</sup> Pick,<sup>1</sup> Novak,<sup>12</sup> and with Gates, Warren, and Warvi<sup>2</sup> that the tumor is essentially benign. The latter group of authors state, "We are in doubt as to the propriety of considering any of these tumors of the apocrine glands as carcinoma in view of their apparently invariable benignity." Gates, Warren, and Warvi say that carcinoma of the sweat glands has been described on a basis of anaplasia and histologic invasiveness but that metastasis is exceptional. It would be unfortunate if the impression should become widespread that these tumors are malignant. This would cause at least some of the patients who have them to be subjected to needlessly radical surgery.

Adenocarcinoma, apart from tumors originating in Bartholin's gland, is occasionally, although infrequently, seen. In one of the cases in this group such a tumor was present. This patient entered the hospital four times from 1938 to 1941. When first seen the tumor was a small node on the labium minus. It recurred after removal and extended slowly, finally involving the neighboring area widely. Clinically this was definitely cancer although of a slowly growing type. Metastasis was not clinically demonstrable. As death occurred in a home for old people no autopsy could be obtained. It was microscopically moderately invasive but mitotic figures were infrequent. While it cannot be asserted positively that it arose from a sweat gland it is probable that it did. In Novak's series are presented two cases of adenocarcinoma of possible although not certain sweat gland origin. Eichenberg,<sup>2</sup> in 1934, reported a case

Fig. 7.

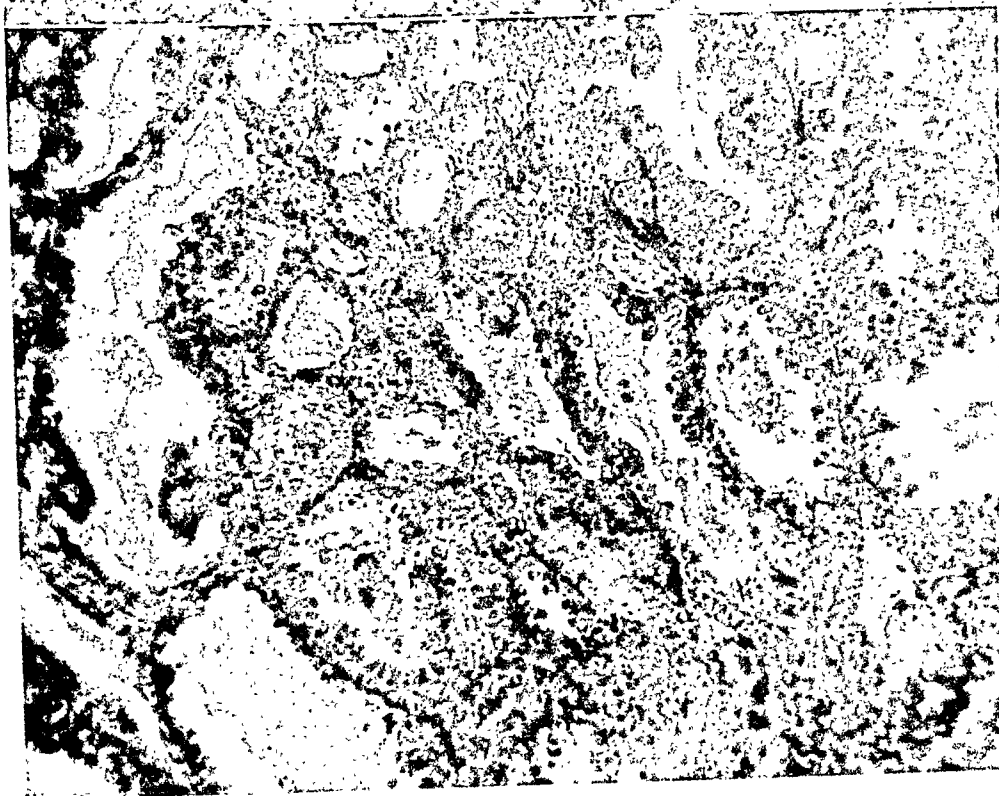
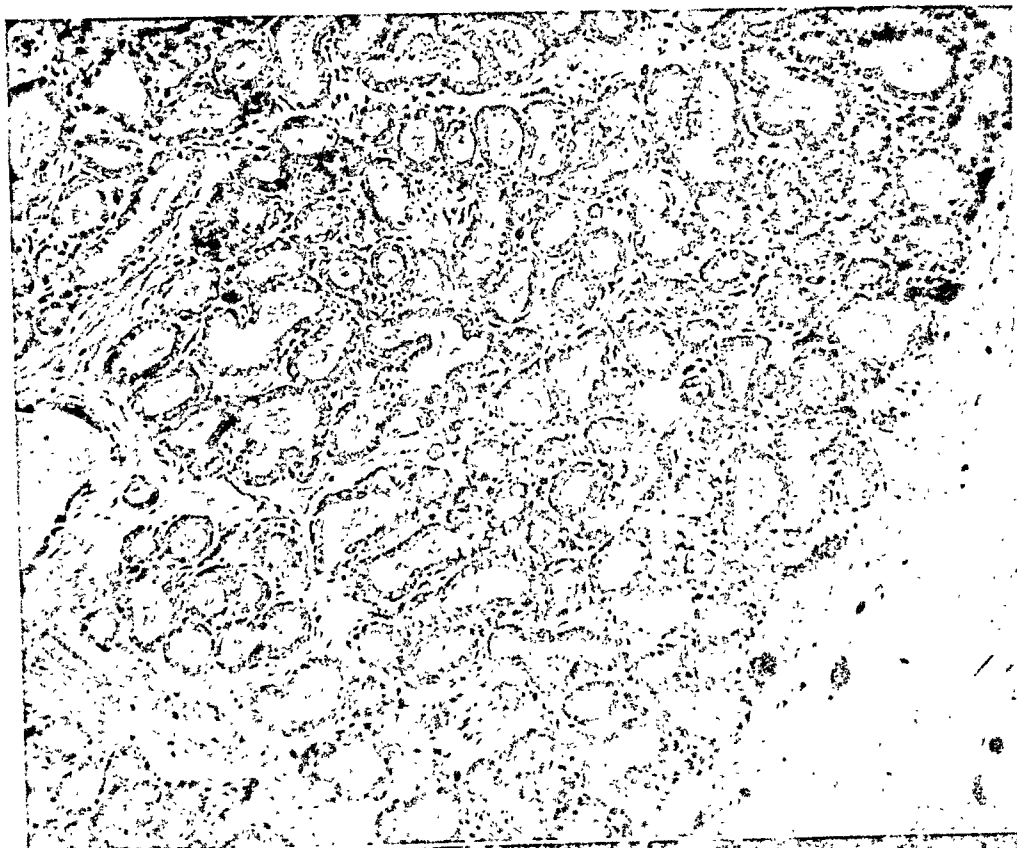


Fig. 8.

Fig. 7.—Multiple layers of epithelium seen in places, as in upper left-hand corner. Cystic dilatation of some glandular spaces. Case of Dr. H. C. Taylor, Jr. ( $\times 120$ )

Fig. 8.—Low-grade adenocarcinoma probably developed from sweat gland. Wide local invasion. Case of Dr. W. C. Danforth. ( $\times 150$ )

## Discussion

DR. JOHN HUFFMAN, Chicago, Ill.—Dr. Danforth has given us a lucid and comprehensive discussion of an unusual clinical and pathological entity. The genesis and histologic structure of sweat gland tumors of the vulva place them among the most interesting neoplasms encountered in gynecologic pathology. Histologically, these tumors are usually described as arising from the apocrine glands. As Dr. Danforth has said, morphologically sweat glands are of three types: the merocrine glands in which the epithelial cells remain intact during the secretory process; the apocrine glands in which portions of the cell cytoplasm are extruded with the secretion; and holocrine glands in which degenerated cells of the epithelium lining the glands make up much of the secretion. While this classification, suggested by Maximoff, is a practical one, Novak and Stevenson have pointed out that there are all sorts of histological and functional gradations between the three types of sweat glands. These gradations must, undoubtedly, make it difficult at times to decide definitely that a particular tumor has arisen from an apocrine rather than a merocrine vulvar gland. Both types of glands are present in the vulvar skin. The histologic similarity between the vulvar tumors and intraductal papillomas of the breast, a holocrine gland, is so close that Cunningham and Hardy have stated that they are indistinguishable from one another. Since, therefore, some uncertainty will probably exist as to the origin of specific tumors it is gratifying that Dr. Danforth has used the inclusive term "sweat gland tumors of the vulva" for the title of his paper. It is one with which no one will disagree. The term hidradenoma, originally used by Pick to designate one of several varieties of sweat gland tumors, has become an accepted term in gynecologic pathology. It is not, however, one that will cling to the student mind and is not photographically descriptive. This would seem a timely place not only to applaud Dr. Danforth's use of a proper anatomical term but to plead for the more widespread application of an easily understood definitive nomenclature in gynecologic pathology.

After reading Dr. Danforth's paper and reviewing some of the pertinent references to which he has drawn attention, it seems evident that we must be cautious in accepting the diagnosis of an adenocarcinoma of the vulva of sweat gland origin from the general pathologists. It would appear that most of these neoplasms are benign but a microscopist unacquainted with their bizarre architectural pattern may easily and understandably discover in them things which are, to him, stigmas of cancer. As Dr. Danforth has pointed out, such an unfortunate error would subject some patients to unnecessary radical surgery.

of carcinoma arising from a hidradenoma. The possibility of cancer must be admitted but the great majority of these tumors are benign. The location on the labium minus would not completely exclude the possibility of sweat gland tumor. The close relationship of apocrine and sebaceous glands and the presence of sebaceous glands on the minor lip would suggest at least the possibility of such a location. In one of our cases a portion, at least, of a sebaceous gland is included in the area occupied by a hidradenoma. The case of Schickele, one of Novak's cases, and one of ours present such a location. The immediate development of adenocarcinoma, without intervention of a hidradenoma, as Novak has suggested, is at least theoretically possible. It is quite possible that this took place in our Case 6.

That these tumors may be found in areas other than those named as their most frequent locations is evidenced by a specimen recently obtained through the courtesy of Dr. John McCarter, Assistant Professor of Pathology at Northwestern University and Director of the Abbott Memorial Laboratories of the Evanston Hospital. This was found at autopsy on the shoulder of a male individual. The microscopic picture is quite typical of hidradenoma.

### Conclusions

1. Hidradenoma is infrequently found in the operating room and laboratory. It is probably far more prevalent than clinical and pathological experience would indicate.
2. The great majority of these growths are benign.
3. Simple excision is quite sufficient for most of them. The exceptional tumor which is, or which becomes, malignant will need more radical attention.
4. The multiple layers of the epithelium of the tumor, which are typical of the gland from which it springs, should not be assumed to be evidence of malignancy.
5. Six cases are reported. Attention is called to the characteristic double-layered epithelial lining of the gland from which the tumor arises and which is reproduced in the tumor.

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method. With the developing tendency to ignore the blood levels as an index of therapeutic effectiveness, this phase of the work was not carried to completion.

Cervical cultures were taken from certain patients with puerperal fevers and from afebrile treated cases but the results were difficult to interpret.

In cooperation with the Department of Ophthalmology many of these patients had antepartum cervical cultures and their babies' conjunctivae were cultured at birth. This portion of the study was directed toward determining the value of penicillin, as compared with silver nitrate, in gonorrheal eye prophylaxis. The final results will be published elsewhere.

The control series (A) totaled 430 patients and the experimental group (B) 465. There were 441 children (11 twins) in A and 472 (7 twins) in B. The distribution according to parity was approximately the same in both series, 185 primiparas and 245 multigravidas in A, as against 214 primigravidas and 251 multigravidas in B. Likewise, the distribution according to financial status was the same; there being 47.4 per cent indigent, 17.6 per cent clinical pay, and 34.9 per cent private in A group, as against 49.0, 16.5, and 34.5 per cent, respectively, in B. There was also no significant difference in age distribution or in the number of complicated labors or pregnancies (Table I).

TABLE I. COMPLICATIONS OF PREGNANCY AND LABOR

	GROUP A CONTROL SERIES	GROUP B PENICILLIN SERIES		
		600,000 UNITS	900,000 UNITS	TOTAL
<i>Complications of Pregnancy.—</i>				
None	369	174	231	405
Placenta previa	2	1	3	4
Premature separation	5	9	2	11
Toxemia	24	10	8	18
Diabetic	2	0	5	5
Eclampsia	2	3	1	4
Syphilis	8	1	3	4
Pyelitis	0	3	0	3
Heart disease	4	3	2	5
Multiple pregnancy	11	2	5	7
Miscellaneous	17	4	7	11
<i>Complications of Labor.—</i>				
None	260	132	167	299
Postpartum hemorrhage	15	9	5	14
Prolonged second stage	51	15	30	45
Prolonged labor	7	9	10	19
Premature labor	55	17	21	38
Intrapartum fever	42	17	24	41
Prolapsed cord	3	4	1	5
Miscellaneous	5	0	7	7

Despite all attempts to select every other patient, the tendency of the nurses to put the more complicated cases in the treated group is evidenced by the inclusion of only seven prolonged labors in the control group as against nineteen in the penicillin series. Third-stage complications, intrapartum fevers, and prolonged second stages were proportional in both series.

The incidence of induced labor was high in both groups for reasons explained in papers by Plass<sup>2</sup> and Keettel.<sup>3</sup> In A, 24.4 per cent of the labors were induced with premature artificial rupture of the membranes, as compared to 31.1 per cent in B. Additional sterile pelvic examinations were deemed necessary in 13.9 per cent of A and 14.2 per cent of B. The incidence of premature spontaneous rupture of the membranes was nearly the same in the two groups.

The method of delivery is indicated in Table II. The incidence of spontaneous delivery was 77.8 and 75.1 per cent, respectively. The difference in

## AN EVALUATION OF PROPHYLACTIC PENICILLIN ADMINISTRATION TO PARTURIENT WOMEN\*†

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THE effectiveness of penicillin in combating postpartum infections has suggested its use prophylactically during labor. The drug has already been used by Odell and Plass<sup>1</sup> in the control of intrapartum infections with considerable benefit to both mother and child. On the basis of these casual observations, it seemed advisable to learn more accurately if penicillin administration during labor and the early puerperium would produce a significant reduction in the number of puerperal fevers. This study was directed at ascertaining this information by means of controlled experimental use of the drug.

The patients were delivered in the Department of Obstetrics and Gynecology of the State University of Iowa Hospitals between Feb. 3, 1947, and Feb. 1, 1948. So far as was practicable, alternate patients as determined by the delivery room nurse received prophylactic penicillin\* according to a predetermined schedule. The only patients excluded were those delivered by the abdominal route and those receiving penicillin therapeutically prior to the onset of labor. All patients were delivered under similar delivery room technique by medical students, residents, or the senior staff. Postpartum temperatures were taken by mouth every four hours (excluding 2:00 A.M.) during labor and the postpartum stay, which averaged from six to nine days.

Until December, 1947, penicillin suspended in beeswax and oil was injected intramuscularly into the gluteal regions. Subsequent to that date, the preparation used was penicillin G in oil and wax, which remained fluid at room temperature and was easier to inject. In the first half of the experimental series each dose consisted of 300,000 units, while in the second half the first dose was 600,000 units and repeated doses were 300,000 units. Each dose was given as a single intramuscular injection. The first injection was given as soon as the patient was definitely in labor. If labor was prolonged for more than twenty-four hours, the injection was repeated at twenty-four-hour intervals until delivery. The single postpartum dose was given twenty-four hours following the last antepartum injection. On the average the antepartum injection was given four to six hours before delivery and the postpartum injection eighteen to twenty hours after delivery.

Blood penicillin levels were determined in 61 women at various times after the injections. Fetal blood levels and amniotic fluid levels were determined in a number of cases. All determinations were performed according to the Kolmer

\*All penicillin was generously supplied by E. R. Squibb and Sons.

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The incidence of two-or-more-day fevers was materially reduced in the treated series, there being 44 in the control and 22 in the treated (10.2 and 4.7 per cent, respectively). When those receiving 600,000 units and 900,000 units are compared, the incidence of two-or-more-day fevers is 6.9 per cent and 3.0 per cent, both statistically lower than the control group. During the past several years puerperal morbidity has been consistently between 10 and 12 per cent at the University Hospitals.

The incidence of intrapartum fever was not materially different in the two groups, there being 42 cases in A as compared with 41 in B. The postpartum course of patients with intrapartum fever was afebrile in 28 of the control group and 31 of the penicillin series.

Clinically significant fevers were infrequent in both groups but were twice as common in the control series. Many intrapartum and one-day fevers occurring within twenty-four hours of delivery are evidently not due to infection but rather to an extragenital factor, possibly dehydration.

The causes of the postpartum fevers were assigned according to the usual clinical evidence. Endometritis was three times as common in the control group (Table IV); the difference was even more marked among those receiving 900,000 units (1.5 per cent as compared with 9.4 per cent in the control series). Mastitis and pyelitis were more common in the treated series; the conduct of labor can scarcely have any etiologic significance.

TABLE IV. CAUSE OF FEBRILE PUERPERIUM

	GROUP A CONTROL SERIES	GROUP B PENICILLIN SERIES		
		600,000 UNITS	900,000 UNITS	TOTAL
Endometritis	40	9	4	13
Pyelitis	1	2	2	4
Mastitis	3	3	2	5

Patients with puerperal infections received definitive treatment according to their needs. Twenty-five in A were sufficiently ill clinically to require penicillin; in the prophylactic group (B) only six required subsequent penicillin therapy. These six patients were treated for mastitis that developed late in the hospital stay. Fevers were of longer duration in the control series, twelve persisted for four days, as compared with two in the Group B. In general, the highest temperature during the febrile period was not materially different in the two groups.

The only reaction to the injections was mild urticaria in seven cases. Two patients who received 600,000 units had general urticaria eight to twelve days after the last medication, while among those receiving 900,000 units there were only five local allergic manifestations. There were no abscess formations at the sites of injections. Discomfort following the injections was relatively uncommon and never severe or persistent.

### Discussion

Aseptic obstetric techniques are directed toward preventing the introduction of pathogenic organisms during labor and at delivery. The postpartum uterus provides an ideal culture medium for bacterial growth. Since penicillin is essentially bacteriostatic, maintenance of an adequate level of penicillin during this period of increased susceptibility should materially reduce the incidence of endometritis. Our results, particularly with the larger dose schedule, appear to justify this hope, but a larger series is desirable.

forceps rotations and midforceps is accounted for by the increased number of prolonged labors in the penicillin series. Analgesics, anesthetics, and number and type of perineal repairs were comparable.

TABLE II. METHOD OF DELIVERY

	GROUP A CONTROL SERIES	GROUP B PENICILLIN SERIES		
		600,000 UNITS	900,000 UNITS	TOTAL
Spontaneous delivery	334	152	197	349
Low forceps	73	35	42	77
Forceps rotation and mid-forceps	16	12	13	25
Spontaneous breech	11	2	11	13
Breech extraction	6	1	5	6
Destructive procedure	0	2	0	2
Version extraction	1	0	0	0

Penicillin serum levels within the so-called range of therapeutic effectiveness were obtained with both dosages, but were higher after 600,000 units. The fetal levels averaged about half the maternal. Penicillin serum determinations, unlike many blood chemistry tests, are not a measure of the precise amount of antibiotics in the circulation. The reported values are interpolations based upon the ability of the serum to inhibit the growth of a standard bacterial culture in vitro, and are at most only rough estimations of the quantity of penicillin in the blood at the time the sample is drawn. Even the most reliable determinations of penicillin blood levels may err by 50 per cent or more. In the average case, it would seem that clinical progress is the better guide to dosage and is more dependable than serum penicillin levels alone.

In the control series, there were twelve stillbirths, or 2.7 per cent, and 2.9 per cent neonatal deaths; in the treated group these figures were 1.9 per cent and 2.5 per cent, respectively. All babies weighing 1,000 Gm. or more were included. Twelve deaths in A and five in B involved children weighing less than 1,500 Gm.

Fevers were designated as "one day" when the elevation of temperature did not persist for more than twenty-four hours; temperature elevations occurring during the first twenty-four hours were included. The "two-or-more-day" fevers included temperature elevations occurring on any two or more days during the puerperium, excluding the first twenty-four hours. Intrapartum fevers were diagnosed when the temperature was 100.4° F. or higher during labor. On the basis of these criteria, the puerperal courses of the women in the two series are shown in Table III.

TABLE III. FEVER DURING PUERPERIUM

	GROUP A CONTROL SERIES	GROUP B PENICILLIN SERIES		
		600,000 UNITS	900,000 UNITS	TOTAL
Afebrile	341	169	230	399
1 day fever	45	19	25	44
2 day fever	25	9	5	14
3 day fever	7	4	2	6
4 day fever	9	1	1	2
5 day fever	2	0	0	0
6 day fever	0	0	0	0
7 or more	1	0	0	0

Some of the intrapartum and early one-day fevers may well be due to dehydration rather than bacterial invasion. This is suggested by the low incidence of subsequent fevers in both groups despite the administration of antibiotic drugs to Group B. The fact that some intrapartum fevers did not respond to penicillin and the occasional puerperal infection did develop despite its prophylactic administration may be explained on the basis of resistant organism, inadequate dose schedule, or mutation of the organisms.

The apparent effectiveness of prophylactic penicillin injections is well illustrated in Fig. 1. This patient, L. T., was delivered by midforceps after Dührsen's incision following a labor of 83 hours and 35 minutes. Penicillin was given daily during parturition and once after delivery. The puerperium was afebrile except for a single elevation of temperature to 100.8° F. fourteen hours post partum.

The puerperal course of P. B. (Fig. 2) illustrated the type of febrile response so frequently encountered in similarly complicated cases in the Group A controls.

This series is too small to permit an evaluation of the effect of penicillin administration in the prevention of neonatal deaths. However, the presence of therapeutic levels in the amniotic fluid would suggest that the sequelae of severe amnionitis, such as intrauterine pneumonia and septicemia, may be materially reduced.

Eastman<sup>4</sup> has given intramuscular penicillin prior to delivery and to the child after birth for gonorrheal eye prophylaxis with encouraging results. Our results do not permit any conclusion but the question is being subjected to further study.

### Conclusions

These results suggest that penicillin may be given profitably to any woman with intrapartum fever, prolonged labor, postpartum hemorrhage, or difficult operative delivery. With the reduced cost and the ease of injecting large doses of penicillin-in-oil or combined with procaine its prophylactic use may be justified. It is certainly a more logical adjuvant to aseptic delivery-room technique than other suggested prophylactic procedures and our results indicate that it can be expected to reduce the incidence of puerperal infections, especially in women with complicated labors and deliveries. Its value in gonorrheal prophylaxis in the infant and in reducing neonatal mortality is equivocal.

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### Discussion

DR. L. M. RANDALL, Rochester, Minn.—Fleming announced the discovery of penicillin in 1929. There followed much in vitro experimentation and it was not until 1940 that Chain first reported in vivo work on the mouse. Since then we have all watched developments. One has only to remember the cases of postabortal and postpartum infections of the prechemotherapy and antibiotic era to appreciate this presentation. Fortunately, most of the organisms responsible for intra- and postpartum infections are susceptible to penicillin. Fortunately, also, unfavorable reactions to penicillin, immediate or remote, are rare and usually not significant. Perhaps these reactions will be somewhat

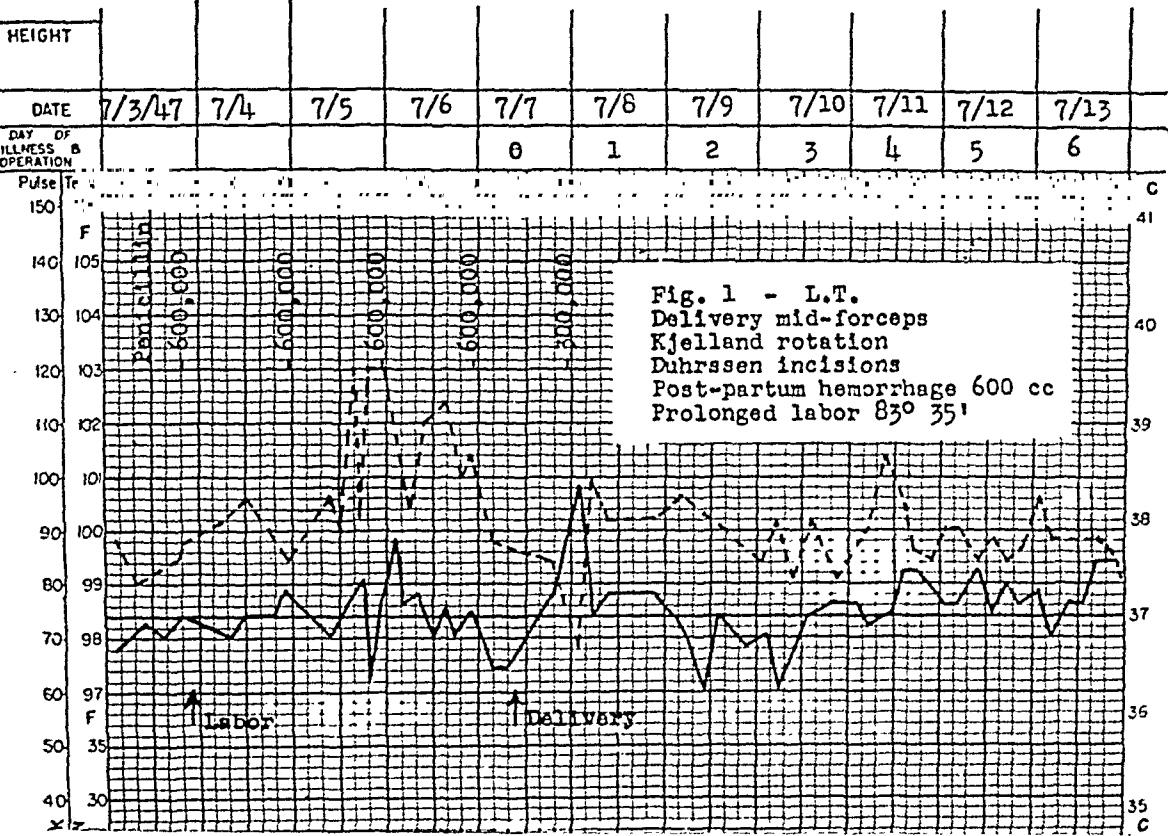


Fig. 1.

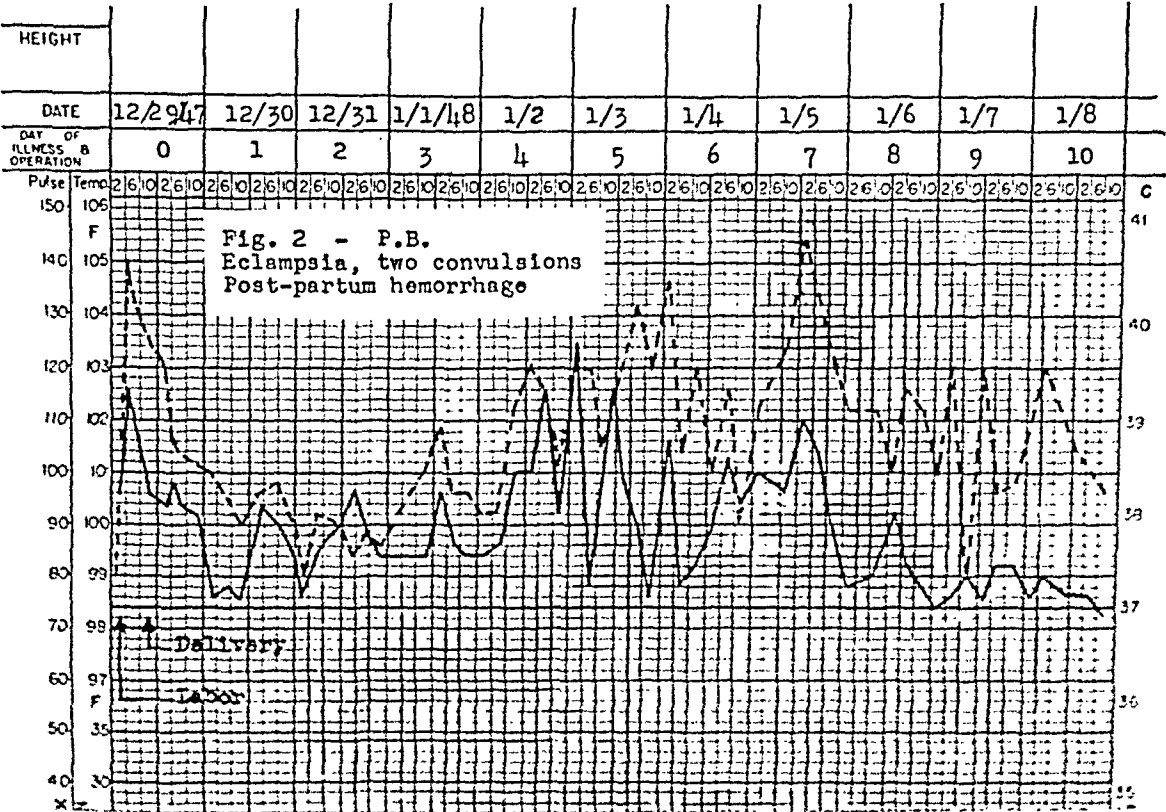


Fig. 2.

DR. RALPH A. REIS, Chicago.—This careful report from the University of Iowa is interesting and provocative. It carries me back to 1935 when Prontosil first came out as a form of chemotherapy. We all jumped on the bandwagon. We all used it therapeutically and then we used it prophylactically. It was used in every cesarean section and every vaginal delivery. Then we began to get reactions such as leucopenia and serum reactions, and as a result prophylactic chemotherapy has pretty well gone into disuse. It has died out completely with us.

We are now in that same stage with penicillin. I am afraid if many reports of prophylactic penicillin get out to the general practitioner and to our resident staffs that this will have a tendency to make them careless. We find breaks in technique, and when we criticize our house staff, the answer is, "Well, we have put her on penicillin." Now, I don't know what the reactions of most men are, but I know that we see a certain definite incidence of real anaphylaxis following the administration of penicillin. We have at our hospital, a physician who has had a severe case of continued generalized urticaria for ten months from a single five hundred thousand unit dose of penicillin. I have two other patients who have recurring urticaria from so-called prophylactic penicillin.

I still believe that the way to avoid infection is to do good careful obstetrics. I still feel that we should stop teaching our interns and residents the phrase "sterile vaginal." I have never been able to do one and I know that no one in this room has ever done a sterile vaginal. There is no such thing. One point at the end of the paper intrigued me greatly: the essayist said that penicillin is bacteriostatic; it is not bacteriocidal. We all agree with that. If you follow a large enough series, you will have the same experience—namely, a little less fever at the time of delivery, but an average or higher incidence of late infections; for when the bacteriostatic effect of the penicillin is gone, there develop late or delayed infections, such as mastitis, residues in the pelvis and pyelitis, etc. I therefore believe that if we are to use prophylactic penicillin—and I am firmly convinced we should not—we have to be prepared to see and treat more late infections.

DR. R. S. SIDDALL, Detroit, Mich.—At Herman Kiefer Hospital we are giving penicillin experimentally before delivery in one-half of our patients who have premature rupture of the membranes or who are in labor for twenty hours or more, or both. We, therefore, are dealing with a group of patients who are often actually or potentially infected. Our dosage also differs from that of the essayists, since we start with only 30,000 units and repeat every three hours until delivery. A few receive many doses, a few others only one, perhaps. Moreover, to make the test more clearcut, we give no penicillin or other therapy after delivery in either the treated or the untreated group unless and until there is definite infection as evidenced by two or more days with temperature elevations to 100.4° F. or over. The untreated patients serve as controls.

We also have noted a tendency to place the more sick patients on penicillin prophylaxis. Consequently, the treated and the control groups are not strictly comparable. Actually, this fact tends to emphasize the only inference which seems justifiable as yet from a review of the 140 treated and untreated cases to date. Apparently patients with infection during labor who receive penicillin are protected to some degree against puerperal infection later. A temperature elevation in labor to 100° F. or above when associated with microscopic evidence of inflammation of the placenta was accepted as indicating definite intrapartum infection. Those without penicillin antepartum had subsequently a 26 per cent incidence of puerperal infection, whereas the figure for those treated was about 17 per cent. Admittedly, this result is not all that could be desired. However, if the essayists' observations and ours are confirmed, it would seem that prophylactic penicillin is definitely indicated in prolonged labor and early rupture of the membranes.

DR. E. F. SCHNEIDERS, Madison, Wis.—Personally, I have noticed that the essayist and the discussants have presented a cross-section of results and impressions obtained in institutional work. I represent in my own practice a "trouble-shooter." Our hospital, which is an open staff hospital, has on its staff 54 physicians who are allowed to bring

increased when the injected material is in a vehicle designed to secure an effective twenty-four-hour level but the convenience and effectiveness of this means of administration far outweigh this small percentage of reactions. No therapeutic agent yet available presents such a large margin between therapeutic effectiveness and toxicity. Dr. Keettel has stated that aseptic technique is still a vital part of delivery-room care and it should continue to be so in spite of the protection afforded by the sulfonamides and antibiotics. He draws attention also to the prepartum elevations of temperature that are not due to infection but are produced by fatigue and dehydration. Penicillin may well be administered prophylactically to these patients for perhaps their resistance to infection will be lowered but we must not forget that relief of pain, and proper nutrition, and hydration of the patient in labor are very important. Our experience and that of others with the prophylactic use of penicillin coincides with that of the essayist. It must be remembered that penicillin diffuses through the placenta and becomes available to the fetus. Examination of blood from the umbilical cord has revealed it to contain an amount of penicillin which was approximately half the amount present in the mother's blood. Hence the welfare of the fetus may be considered when penicillin is administered prophylactically. Recently Eastman, as a corollary to his study on ophthalmia neonatorum, reported a puerperal morbidity of 3.8 per cent among the mothers receiving penicillin compared to a morbidity of 9.2 per cent when penicillin was not administered. He found that 75 per cent of cultures from the uterine cavity taken post partum were sterile when penicillin had been administered. This would correlate with the marked reduction in puerperal endometritis reported by the authors. One may emphasize early and adequate dosages of penicillin, the desirability but not the necessity for a bacteriologic diagnosis, the importance of an accurate clinical estimate of the patient's condition, continuation of the penicillin for at least three days post partum in potentially infected cases. It may be noted that no deleterious effect from the administration of penicillin has been noted on the fetus, the genital tract, or the pregnancy. Penicillin is not a panacea for all infections and the combination with sulfonamide and occasionally with streptomycin should be kept in mind; however, the latter should be reserved for cases in which the susceptible causative organism has been identified.

DR. E. STEWART TAYLOR, Denver, Colo.—As usual, Dr. Plass' department in its approach and in the results obtained adds materially to general obstetrical policy and practice. Penicillin for women with intrapartum fever, prolonged labor, or difficult delivery is a distinct adjunct. Penicillin reaches the fetus and is of prophylactic benefit to the unborn child and to the child in the nursery. The coli and other gram-negative bacilli are not affected by penicillin, and these organisms are often the causative agents concerned with sepsis in the newborn. For this reason we have given sulfathiazole and penicillin to those mothers whose labor may be complicated by infection. In a recent article in the *Journal of the American Medical Association*, September 11, by Ambrose and Levy, they reported an interesting observation. They have noticed that continued administration of penicillin to a patient with pneumococci pneumonia will allow the recovery of coli bacilli from the sputum of the patient after the pneumococci have disappeared.

Apparently penicillin affects other organisms and enzymes of the body so as to allow the coli bacilli to multiply at unusual and abnormal sites. Two cases from our service illustrate this point. A mother with prolonged ruptured membranes was given penicillin prophylactically. The offspring was in good condition and was given penicillin to protect it from the infection that may have resulted from prolonged rupture of the membranes. The infant seemed normal until the sixth day when it suddenly showed signs of meningitis and died soon thereafter. The cause was *B. coli* meningitis—this after the use of penicillin prophylactically. A second infant developed multiple subcutaneous abscesses in the nursery from which *B. coli* were recovered while this infant was receiving intramuscular penicillin injections for postpartum infections. These complications may have been the result of penicillin destroying certain pathogens and enzymes necessary to the regulation and deterrence of normal coli bacilli growth and control.

prophylactically used penicillin and sulfadiazine were employed before performing the cesarean section. It is my firm belief that we will be employing the extraperitoneal cesarean less and less. I also believe cesarean hysterectomy is going to be an outmoded procedure when employed to prevent sepsis.

DR. KEETTEL (Closing).—There are several points I would like to emphasize. The first is that we consider this a preliminary report. We realize the controversial nature of this subject but believe the only way to find out whether penicillin is of value in abnormal labors is to conduct carefully controlled experiments on normal patients.

We are continuing with another experiment along slightly different lines, and now have about three months' experience with the new project. In this investigation we are giving the same dosage of penicillin but are using indigent patients as the treated group and private and clinical-pay patients as the control group. We are studying the effect of prophylactic penicillin on neonatal deaths and puerperal morbidity but, in addition, are evaluating its value in eye prophylaxis. With permission of the State Health Department, we are using no eye prophylaxis except penicillin given to the mother. We will report on this later on.

maternity cases into the hospital. Over a period of a little over three and one-half years we have accumulated somewhat better than 5,500 consecutive cases without one maternal death from any cause whatsoever. The last death resulted from a case that had a hopeless leucemia. The next-to-last case came into the hospital with a hemiplegia due to a cerebral hemorrhage secondary to a neglected eclampsia. The third case died from hemorrhage. This death would have been prevented had the blood bank been in operation at that time. Because of some transfusion reactions it was temporarily out of operation.

But since that time we have had over 5,500 consecutive cases without one maternal death from any cause. Prior to the advent of penicillin and sulfadiazine our results were almost as good, comparatively speaking. I mean as measured from the standpoint of the mother. They were not as good, however, as regards the welfare of the infant. I desire to refer to a number of infant deaths within hours or within days with a full-blown pneumonia that they had acquired during these prolonged labors with ruptured membranes. These infants were infected with and died of a pneumonia which the pathologist classified as having been in process of development over a period of several days. Many of these cases are brought in when they have been in labor for many hours and then we have to correct certain faults.

However, I have no doubt in my own mind but that the combination of penicillin and sulfadiazine, and I mean intravenous sodium sulfadiazine, in some of these precarious cases helps, because we know then what the absorption is, we know what the patient is getting, and we can regulate the dosage with blood levels, and we can bring it up to the optimum and keep it there, particularly if the patients are vomiting. Adjunct therapy with plasma and/or blood, saline, glucose, and so forth, we must not forget. Our percentage of cesarean sections is only 2.6 per cent over a period of twenty years, and still our results have been good because of the fact that we try to continue to maintain the highest standards of obstetrical care. We do use the adjunct value of penicillin and sulfadiazine in these complicated cases. We have given up completely the use of penicillin-in-wax or penicillin-in-oil but are using the crystalline preparations in preference because we find far fewer reactions, nowhere near the degree that has been mentioned.

DR. A. J. KOBAC, Chicago, Ill.—At the Cook County Hospital we have been delivering over 600 patients every month and the problem of sepsis and septic morbidity has always been a very potent one. We have found the use of penicillin and sulfonamides to be a very beneficial one when sepsis has occurred. I would like particularly to dwell upon the use of penicillin prophylactically when a cesarean section is performed. Before 1947, when we did not use penicillin or sulfonamides prophylactically we were extremely reluctant to perform a transperitoneal cesarean section, and thereby lost many babies; and when we did perform a cesarean section it was a Porro hysterectomy, and later as an alternative an extraperitoneal section using the technique of Waters.

Since 1947 and up to the present time we have not performed any more cesarean hysterectomies except for fibromyomas, or Couvelaire uterus, and now we rarely perform the extraperitoneal cesarean section but instead we employ the low cervical type of cesarean and rely on prophylactic use of penicillin with or without additional sulfonamides. We frequently used whole blood because at the County Hospital many of our patients have blood deficiencies, and we have found that whole blood is extremely beneficial when employed in conjunction with penicillin.

I have recently gone over the records of about 25 patients and there are more histories to be reviewed. I have found these 25 patients particularly interesting because they were patients who were potentially infected and we would never have dared to perform a transperitoneal low cervical section because many had prolonged labors or had prolonged ruptured membranes. Nevertheless we have found that our postoperative morbidity was just as satisfactory as the morbidity of those patients where we did an extraperitoneal section. Our results were far from gratifying in the patients who had an extraperitoneal cesarean operation. This is in accord with an article that has recently appeared in the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY* by Douglas and Lander-man, where the



was a drop in serum proteins early in pregnancy, which was somewhat modified toward the end of pregnancy, and that there was a satisfactory rise in the postpartum period. Plass and Matthew,<sup>33</sup> pursuing the study further, show a drop in the total protein from the onset of pregnancy to the last four weeks, with a rise, but not completely to normal, in the last four weeks. They show, also, that the albumin fraction has a deeper curve of drop than does the total serum protein and is back almost to normal, but not quite, in two weeks post partum. They say that the globulin shows little regular change. Eastman<sup>16</sup> demonstrates that there is a slight relative increase in globulin in the normal pregnancy and that the average A/G ratio is 1.7. Dieckmann and Wegner,<sup>11</sup> using a much larger series of cases than former authors, show that there is a 6 per cent decrease in the protein concentration in pregnancy and 2 per cent more depletion in the first postpartum week, but that serum proteins return to their original value by the fifteenth postpartum day. They state that while the volume per cent decreases, there is an actual increase in the total amount of serum protein per kilogram of body weight when one excludes the weight of the fetus, placenta, and amniotic fluid. Dodge and Frost<sup>15</sup> and Rheinhardt,<sup>34</sup> in subsequent work, fully confirm the previous findings of these authors.

Robinson and Hogden,<sup>35</sup> Kingsley,<sup>24, 25</sup> and Weichselbaum<sup>48</sup> all give excellent methods for the determination of the serum proteins and albumin and globulin fractionation.

There are many discussions in the literature regarding the effect of hypoproteinemia and attendant edema in both pregnancy and nonpregnancy. Strauss<sup>40-44</sup> was one of the first to stress the importance of an adequate protein intake in the prevention of edema and toxemia. Myers and Taylor,<sup>31</sup> several years earlier, discussed the effects of hypoproteinemia as a result of the deficient utilization of proteins either by faulty ingestion or faulty metabolism. Others discussing the effect of hypoproteinemia upon edema are Binger and Keith,<sup>6</sup> Rytand<sup>36</sup> and Messinger.<sup>29</sup>

Cross,<sup>9</sup> in 1929, pointed out that liver function tests show the liver to be under stress during normal pregnancy, and that the stress becomes more intense as the pregnancy progresses, being progressive and greatest in the last trimester and during labor.

Bruckman and Peters<sup>7</sup> state that edema is present in patients with malnutrition only when the serum albumin is below normal, showing that with a serum albumin above 4 Gm. per cent they will rarely have edema, and that they invariably have edema if the serum albumin falls as low as 3 Gm. per cent.

Sullivan et al.<sup>45</sup> found a retention of bilirubin in bilirubin tests for liver function when the liver had been damaged by toxemic states, in what we would now interpret as a protein-depleted liver. Herscheimer<sup>22</sup> makes similar observations in normal pregnancy based upon the hippuric acid excretion test. Dodd and Minot<sup>14</sup> demonstrate that there is a deficiency of serum protein in patients fed on diets which are low in total calories or proteins. Experimental work on animals by Madden and his co-workers<sup>27</sup> and by Weech<sup>47</sup> indicated that dietary hypoproteinemias can be developed and point out the relationship between edema and low serum albumin levels.

Madden and Whipple<sup>28</sup> show that the food proteins furnish the amino acids, and that when they are absorbed from the gastrointestinal tract they are synthesized by the liver cells into the plasma proteins. They further demonstrate that in the absence of liver damage, the ability to build the plasma proteins and hemoglobin comes from the material stored in the liver. Elman and his co-workers<sup>18, 19</sup> believe that in severe hypoproteinemias, unless the serum

# A CORRELATED STUDY OF SERUM PROTEIN, ERYTHROCYTE COUNT, LEUCOCYTE COUNT, HEMOGLOBIN AND HEMATOCRIT IN NORMAL PREGNANCY\*

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THIS study is an attempt to correlate the relationships between the hemoglobin content of the blood, the erythrocyte content, the leucocyte content, the hematocrit data, and the fractional serum proteins.

For material in this series 411 consecutive patients were taken, no selection being made, except to exclude any patient showing a pathological condition which might interfere with her normal progress and development in pregnancy. Otherwise, the study was carried out on consecutive patients as they presented themselves for care. The age and parity relationships are shown in Table I.

TABLE I. AGE AND PARITY

	PRIMIPARAS	MULTIPARAS	TOTAL
Number of patients	281	130	411
Age of patients	23.3 years Range 16-39	26.3 years Range 16-43	24.2 years

*Laboratory Methods.*—The hemoglobin was determined by the Haden-<sup>21</sup> Hausser technique. The erythrocyte and leucocyte counts and hematocrit determinations were made by standard methods. In the beginning of the protein work the Kjeldahl method was used along with the biuret method of Weichselbaum,<sup>45</sup> running Kjeldahl and biuret technique simultaneously on each individual. After sufficient number had been run it was found that there was no variation between Kjeldahl and Weichselbaum techniques, so the Kjeldahl method was then abandoned for the remainder of the series.

The results found may be modified by the fact that all patients who showed any grade of anemia were placed on antianemic therapy, although Talso and Dieckmann<sup>46</sup> demonstrated that there would be but small modification occurring. Also, all patients under discussion were individually attended by one of the authors and were instructed and requested to follow a high protein diet at the first visit. Insofar as these two facts might modify the normal course of pregnancy in relationship to this study, there was interference with the physiological processes.

Stander and Tyler,<sup>35</sup> in 1920, first pointed out that the moisture content of blood increases up to the seventh month of gestation and then remains stationary or rises slightly until term. They show that the erythrocyte count and the moisture content vary inversely. Attention was first focused on the problem of the serum proteins per se in pregnancy by the work of Plass and Bogert<sup>52</sup> in 1924 and the work of Coetzee.<sup>5</sup> These workers found that there

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erythrocyte count, the leucocyte count, the hematocrit, and total serum proteins with their fractions and ratio. This, then, should emphasize to us the imperative necessity of adequate dietary and antianemic therapy in pregnancy.

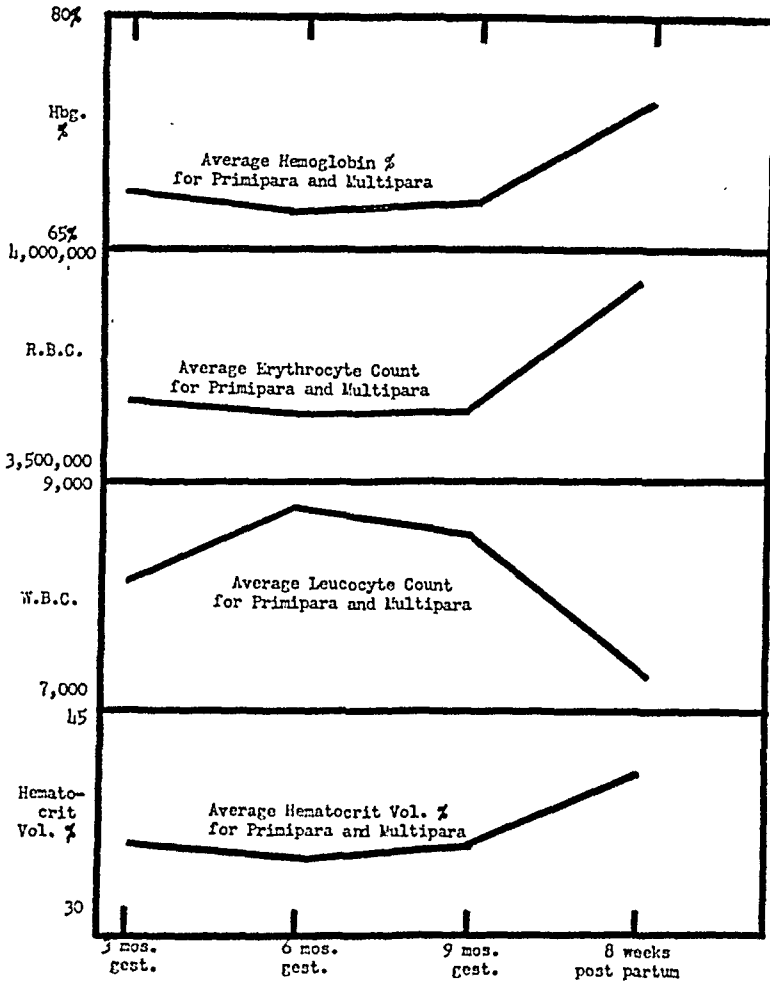


Fig. 1.

In analyzing our results, it was found that in each series of work the hemoglobin, the erythrocyte count, the leucocyte count, the hematocrit, the total serum protein, the serum albumin, the serum globulin, and the A/G ratio values for the primipara and the multipara ran so closely parallel that their average figure was equivalent for each. Accordingly, we have plotted only the averages for the primipara and the multipara so as not to multiply unnecessarily the mass of data available. The values found in the tables and charted in the figures demonstrate that there is a close parallelism between the hemoglobin, the erythrocyte count, the hematocrit, and the total serum protein, i.e., all revealing an appreciable drop from three to six months, a slight rise from six to nine months and a rise above three months at eight weeks post partum. The leucocyte count acted in a reverse manner. The serum albumin shows a marked drop during the pregnancy and a complete return following pregnancy. In contradistinction to the findings of other authors except Eastman<sup>16</sup> our serum globulin figures show a consistent rise

albumin is lowered to such a great extent that the body is unable to meet the depletion effect, the serum albumin rapidly corrects and holds the plasma protein volume up to a level allowing the body to correct the loss. They suggest that the cause of death in these patients is too great a depletion of the albumin fraction. The work of Ebert<sup>17</sup> confirms these findings. Conversely, low protein diets produce liver damage as well as liver damage being a factor in the production of hypoproteinemia. These facts are demonstrated by Beattie and Steele<sup>1</sup> and also by Guorgy.<sup>20</sup> Berryman and Bollman,<sup>3, 4</sup> by producing experimental hepatitis in animals by restriction of diet, reduced the level of the proteins in the plasma mostly at the expense of the plasma albumin. They state that this reflects the functional capacity of the liver more than the dietary deficiency. In a subsequent article they contend that pregnancy causes a lowering of fraction which is reflected in the total serum protein level, and that the concentration of albumin is not markedly affected.

The liver feeding experiments of Whipple and Robscheit-Robbins<sup>40</sup> produced hypoproteinemias with concomitant reduction of protein storage, showing storage of only one-half or one-third of the normal amount of hemoglobin-producing factors in the liver. Their experiments further demonstrate that the important reserve stores for hemoglobin building are in part protein and are jealously guarded by the body even in the face of severe bleeding. The protein intake must be lowered also to lower the storage of the protein fraction of the hemoglobin-producing store. They also found that the values for hemoglobin production in the livers of eclamptic and lactating women are very low, due in the former to the depletion of the disease, and in the latter to the drain on the body economy by lactation.

Bibbs,<sup>5</sup> in his studies, observed that hypoproteinemia was a constant finding in hyperemesis gravidarum and in the late toxemias, and indicated that some women on adequate diets go into hypoproteinemia and toxemia even though the diet be completely adequate. He found no correlation between serum protein and hemoglobin levels nor between anemia and toxemia.

Stead and Ebert<sup>39</sup> proved that exercise causes a decrease in plasma volume and an increase in hematocrit, hemoglobin, and serum protein in both normal and splenectomized human beings. The same effect is obtained by epinephrine administration. They conclude that, although the spleen acts as a blood reservoir in the dog, cat, and horse, it does not do so in the human being.

Miller and Whipple<sup>30</sup> show the protective effect of methionine and cystine (sulfur containing amino-acids) in the protection of the liver in protein depletion states. They emphasize the necessity, therefore, of a high protein and amino-acid intake in the diet as well as a high carbohydrate diet in liver protection. Macarthur's<sup>26</sup> recent cases emphasize the use of methionine, as a sulfur containing amino-acid, in the protection of the liver in the toxemic states of pregnancy. Seeley<sup>37</sup> demonstrated that in protein-depleted animals the feeding of beef protein stimulated albumin production, that casein stimulated both albumin and globulin production, whereas casein hydrolysates (Amigen) stimulated only globulin formation.

With the foregoing facts in mind, it would appear that these statistics should differ from the normal findings in untreated pregnancy, because these patients were all supposed to be on high-protein diets, and all were on standard antianemic therapy. However, these women, in spite of approved therapy, still show typical curves for pregnancy when one plots the hemoglobin, the

TABLE IV. LEUCOCYTE COUNT, RANGE AND AVERAGE DETERMINATION

	3 MONTHS' GESTATION	6 MONTHS' GESTATION	9 MONTHS' GESTATION	8 WEEKS POST PARTUM
Primipara	8,282 Range 4,750-12,900	9,184 Range 4,500-17,800	8,673 Range 3,100-17,300	7,519 Range 3,850-11,550
Multipara	8,250 Range 5,200-11,700	8,477 Range 5,500-12,800	8,582 Range 5,050-14,500	7,368 Range 4,850-10,800
Average	8,190	8,830	8,627	7,443

TABLE V. HEMATOCRIT, RANGE AND AVERAGE DETERMINATIONS

	3 MONTHS' GESTATION	6 MONTHS' GESTATION	9 MONTHS' GESTATION	8 WEEKS POST PARTUM
Primipara	37 Range 26-46	36 Range 29-47	37 Range 29-55	41 Range 34-51
Multipara	38 Range 33-46	36 Range 31-57	37 Range 27-45	41 Range 35-46
Average	37	36	37	41

TABLE VI. TOTAL AND FRACTIONAL SERUM PROTEINS, AVERAGE AND RANGE DETERMINATIONS

	TOTAL SERUM PROTEINS				SERUM ALBUMIN				SERUM GLOBULIN				A/G RATIO			
	3 MO. GEST.	6 MO. GEST.	9 MO. GEST.	8 WEEKS P.P.	3 MO. GEST.	6 MO. GEST.	9 MO. GEST.	8 WEEKS P.P.	3 MO. GEST.	6 MO. GEST.	9 MO. GEST.	8 WEEKS P.P.	3 MO. GEST.	6 MO. GEST.	9 MO. GEST.	8 WEEKS P.P.
Primipara.—																
Average	6.97	6.96	6.91	7.20	4.52	4.39	4.40	4.58	2.45	2.57	2.51	2.62	1.84	1.76	1.77	1.84
Range	6.08 8.00	5.58 7.78	6.08 7.65	6.57 7.86	3.81 5.09	3.20 4.98	3.75 5.13	4.23 5.07	2.27 2.91	2.38 2.80	2.33 2.52	2.34 2.79	1.09 2.69	1.34 2.18	1.32 2.19	1.54 2.23
Multipara.—																
Average	6.98	6.83	6.89	7.23	4.58	4.42	4.37	4.61	2.40	2.41	2.52	2.62	1.87	1.88	1.70	1.81
Range	6.08 7.69	5.99 7.82	6.05 7.65	6.33 8.14	4.27 5.12	3.96 5.26	3.93 4.78	4.21 4.84	1.81 2.55	2.03 2.56	2.12 2.37	2.12 3.30	1.47 2.69	1.44 2.28	1.46 2.14	1.34 2.38
Average	6.97	6.89	6.90	7.21	4.55	4.40	4.39	4.59	2.42	2.49	2.51	2.62	1.85	1.82	1.73	1.82

throughout the pregnancy and an additional rise in the postpartum period. The albumin-globulin ratio, to a large extent, duplicates the serum albumin curve.

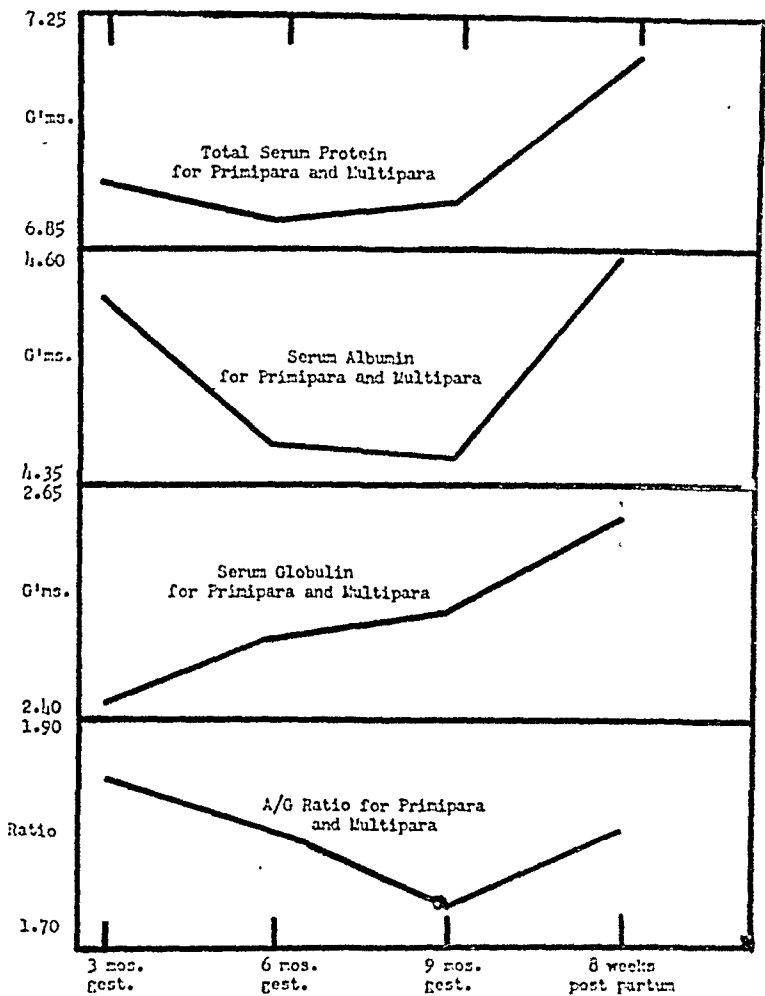


Fig. 2.

TABLE II. HEMOGLOBIN, RANGE AND AVERAGE DETERMINATIONS (IN PER CENT)

	3 MONTHS' GESTATION	6 MONTHS' GESTATION	9 MONTHS' GESTATION	8 WEEKS POST PARTUM
Primipara	70	69	69	75
	Range 54-87	Range 53-84	Range 55-83	Range 66-90
Multipara	71	67	69	77
	Range 58-90	Range 52-80	Range 52-83	Range 67-90
Average	70	68	69	76

TABLE III. ERYTHROCYTE COUNT,\* RANGE AND AVERAGE DETERMINATIONS

	3 MONTHS' GESTATION	6 MONTHS' GESTATION	9 MONTHS' GESTATION	8 WEEKS POST PARTUM
Primipara	3,67	3,61	3,65	3,92
	Range 2,28-4,74	Range 2,72-4,80	Range 2,50-4,52	Range 3,05-4,84
Multipara	3,74	3,53	3,70	3,96
	Range 2,97-4,94	Range 2,58-4,16	Range 2,89-4,40	Range 2,98-4,99
Average	3,69	3,65	3,67	3,97

\*Final four zeros omitted.

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411 ALAMEDA ROAD.

### Discussion

DR. LESTER D. ODELL, Chicago, Ill.—I have nothing further to add concerning the facts. As to their interpretation, there are some things to be said.

It seems doubtful that the hypoproteinemia of pregnancy, particularly during the toxemias of pregnancy, causes the formation of edema. Although some edematous patients have serum proteins below the critical level of 5.5 Gm. per cent, we see patients with edema whose serum proteins are above 5.5 Gm. per cent, and others without edema whose serum proteins are below that figure. Furthermore, the serum proteins may fall to extremely low

### Discussion

It is the feeling of the authors that this series of cases is of sufficient number to make the findings statistically sound. In many of the early series the number of cases, as shown by Dieckmann, are sufficiently small to explain the differences between their findings and these figures.

It was felt that the demonstration of reduction in serum albumin associated with the globulin rise makes it clear why the experimental work on liver damage in protein depletion states is germane to this study. If the work of Sullivan, Herscheimer, Elman, and others which shows the toxic effects of serum albumin depletion upon the liver is accepted, then these figures, which show a serum albumin that is reduced with a concomitant globulin rise, would indicate the importance of prophylactic dietary control of pregnant women. In consideration of dietary control one should not lose sight of the work of Seeley. This would teach us to feed patients beef products with casein as a second choice, and to avoid casein hydrolyates which metabolically yield globulin. In the event of the failure of control by dietary methods, methionine medication as used by Macarthur would be found.

Furthermore, the liver-feeding experiments of Whipple which show the reduction in hepatic storage of the hemoglobin-producing factor in serum-protein, and especially serum-albumin, depletion serve to explain, in company with the hydration effect of Stander and Tyler, the allegedly physiological anemia of pregnancy. Likewise, these facts, plus the increase in total blood volume in pregnancy, explain the therapeutic difficulties involved in the treatment of the anemias of pregnancy.

### Summary and Conclusion

1. Hemoglobin, erythrocyte count, leucocyte count, hematocrit, total serum protein, and protein fraction determinations were made at three months, six months, nine months and eight weeks post partum on 411 cases.

2. The average value for serum globulin was found to show a steady rise during pregnancy and into the postpartum period.

3. During the pregnancy the average values for the total serum proteins fell slightly and steadily until the later part of the pregnancy and then showed a postpartum rise to normal. This drop was entirely at the expense of the serum albumin fraction.

4. The curves for the hemoglobin, the total serum protein, the erythrocyte count, and the hematocrit were found to be almost identical.

5. The so-called physiological, or more properly idiopathic, leucocytosis of pregnancy was demonstrated.

6. The A/G ratio curve was found to approximate the curve of the serum albumin.

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## THE URINARY BLADDER DURING LABOR\*†

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THE distended urinary bladder is often described as a major obstruction to the progress of labor. Moreover, it is pointed out that a full bladder at the time of delivery may cause undue maternal injury. Titus<sup>1</sup> writes, "This may strip loose the fascial attachments of the base of the bladder and the roof of the vagina with subsequent cystocele formation, with or without incontinence." DeLee and Greenhill<sup>2</sup> state that the bladder may "come to lie on the vagina."

By means of postdelivery cystoscopy, Crabtree<sup>3</sup> found evidence of injury in the form of edema which is largely confined to the base and anterior wall of the bladder, as well as its sphincter. Ecchymosis is often present in the mucous membrane of the trigonal portion. Williams,<sup>4</sup> Beck,<sup>5</sup> and Titus indicate the desirability of emptying the bladder before operative or spontaneous delivery. Catheterization is performed at this time in the belief that the procedure will remove obstruction and prevent undue pressure.

On the other hand, when attendants do not interfere, the bladder is rarely empty during the latter part of labor. Complete evacuation is prevented when the urethra becomes compressed by the presenting part. Frequently, the bearing down efforts of the mother are accompanied by small spurts of urine. Catheterization at this time is often technically difficult, and may be unduly traumatizing. Perhaps the retention of some urine at the time of delivery may be physiologic. According to Pascal's law, pressure applied to a liquid at any point is transmitted equally and undiminished in all directions. It is possible that the presence of urine in the bladder may serve to prevent undue pressure to any single part. This same principle is emphasized when the protection which the developing fetus derives from the amniotic fluid is discussed.

Certainly, the degree to which the distended bladder may obstruct the progress of labor, and the pressure exerted upon it have been incompletely investigated. DeLee and Greenhill<sup>2</sup> present a diagram to show the abdominal position of the bladder late in labor. Von Schubert's<sup>6</sup> report contains drawings from x-ray films indicating a similar situation with both vertex and breech presentations prior to delivery. By means of cystograms, Martin<sup>7</sup> showed that the presenting part may compress the bladder against the symphysis pubis. However, in order to evaluate changes in the location of this organ, all phases of labor must be studied.

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†Prize Award paper.

levels post partum, during a period when the patient is losing her accumulated water and sodium chloride. We have administered concentrated human plasma to hypoproteinemic toxemic women without affecting the serum protein level, and without improvement of edema.

Dr. Hamilton has mentioned the level of albumin as a critical factor in edema. He has emphasized the feeding of a high-protein diet to counteract this decrease in albumin. We have checked the protein intake of ambulatory obstetric patients by the simple expedient of measuring the nonprotein nitrogen in a twenty-four-hour urine. This showed that many of them do not eat the 80 Gm. of protein per day that we advise. The administration of electrophorically purified albumin may temporarily elevate the plasma albumin. However, this change is rapidly corrected within twenty-four hours by an increased renal excretion of protein, presumably albumin. We have observed no clinical improvement following its use.

The importance of the liver in plasma protein synthesis is well known. As Dr. Hamilton has pointed out there is some evidence of liver dysfunction during the toxemias of pregnancy. Recently we have obtained multiple liver function tests on normal and toxemic women. During toxemia there are changes which would indicate some liver disturbance, but these are unrelated to the severity of the disease. During normal pregnancy there were no significant aberrations.

As I see it, there are changes in the plasma proteins and blood hematocrit during normal pregnancy. These are probably related to an increased blood volume with consequent hemodilution. Until further evidence to the contrary, I believe they are physiological, not the result of liver disease and probably do not cause edema.

DR. HAMILTON (Closing).—I think Dr. Odell has probably arrived at the same point that I have reached in consideration of the serum proteins, that being one of complete disgust with our methods of determination. I suspect that he feels as I do, that our findings in plasma serum albumin and globulin do not represent the true physiological protein balance of the cells with which we are dealing, and that we are going to have to get a new method of attacking the problem before we are going to understand the proper physiology of the cells involved.

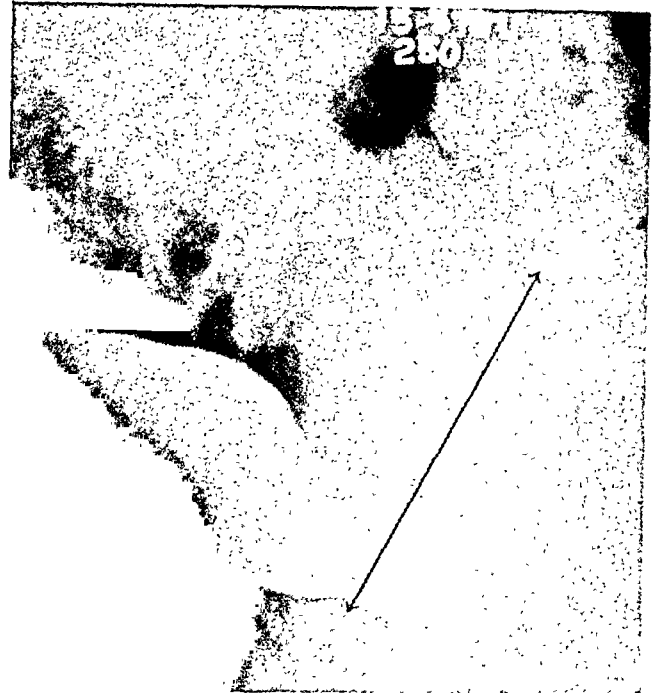
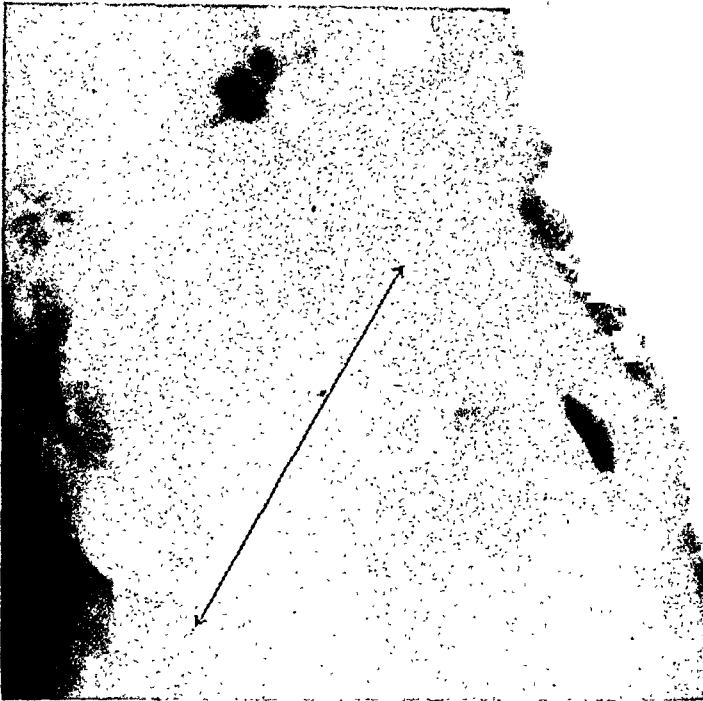


Fig. 2.—At the time of engagement, distention of the pelvic portion of the bladder prevents normal descent.

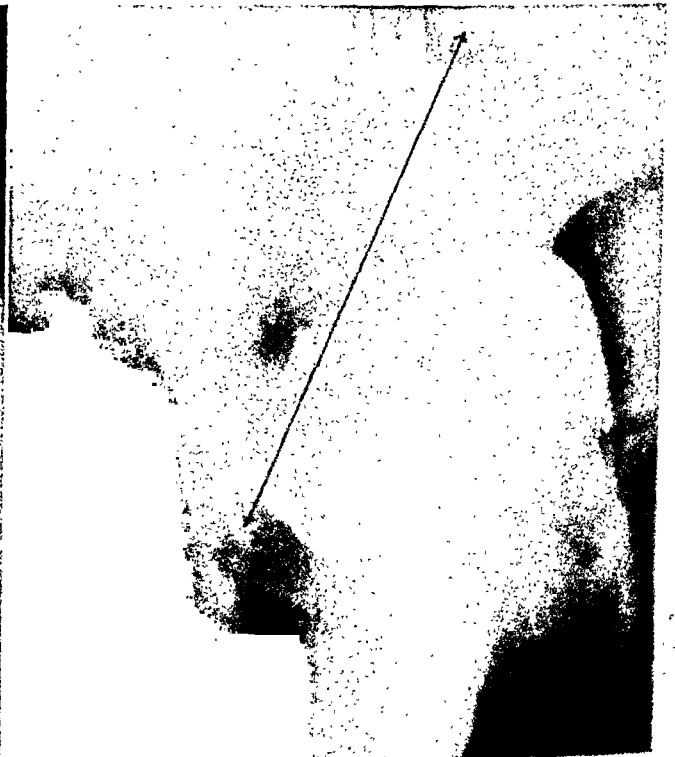


Fig. 3.—The presenting part is disengaged by bladder distention.

The extent to which the urinary bladder can obstruct labor is best demonstrated roentgenographically, while potential injury from compression can be estimated by pressure recordings (cystometric studies) with a water manometer.

### Obstruction to Labor (Roentgenographic Study)

Patients at Parkland Hospital were selected at random to represent the following phases of labor:

- I. Early in labor, prior to engagement.
- II. At the time of engagement.
- III. During labor with the presenting part well past the inlet.
  - A. With cephalic presentation.
  - B. With breech presentation.
- IV. Late in labor with the presenting part near or on the pelvic floor.
- V. Immediately following delivery of the head.
- VI. Immediately following delivery of the fetus.

Three lateral views were made for each patient: (1) an orienting film, (2) with the bladder distended by 150 to 300 c.c. of 25 per cent aqueous sodium iodide, (3) with minimal quantities of the same contrast solution. Anteroposterior and oblique views were of little value for this purpose and were abandoned early in the course of this study.

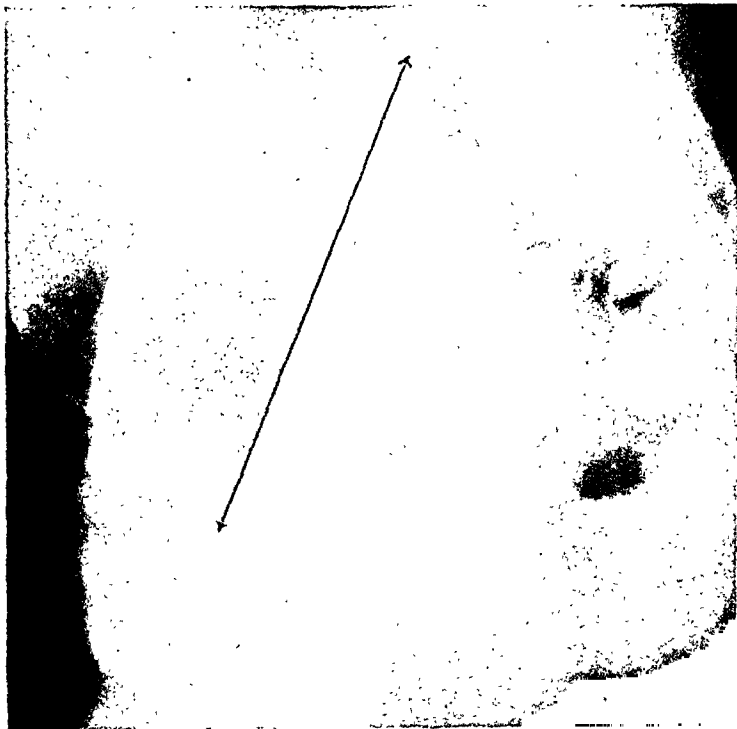


Fig. 1.—Prior to engagement, the distended bladder obstructs normal progress.

### Results

A constant relationship between the location of the bladder and the degree of cervical dilatation could not be demonstrated. The following interpretations are presented from representative films:

I. Prior to engagement, Fig. 1, a large portion of the bladder retained its pelvic status. During this phase, the distended organ did obstruct descent.

II. At the time of engagement, Figs. 2 and 3, a moderate portion of the bladder was in the pelvis. When distended, it did interfere with the normal progress and occasionally the presenting part was disengaged.

III. When the presenting part lay deep in the pelvis, the bladder was mostly abdominal with only a small pelvic portion. If the pelvis was ample and the fetus small, a larger tongue of pelvic bladder was noted. This factor did not alter our general impressions.

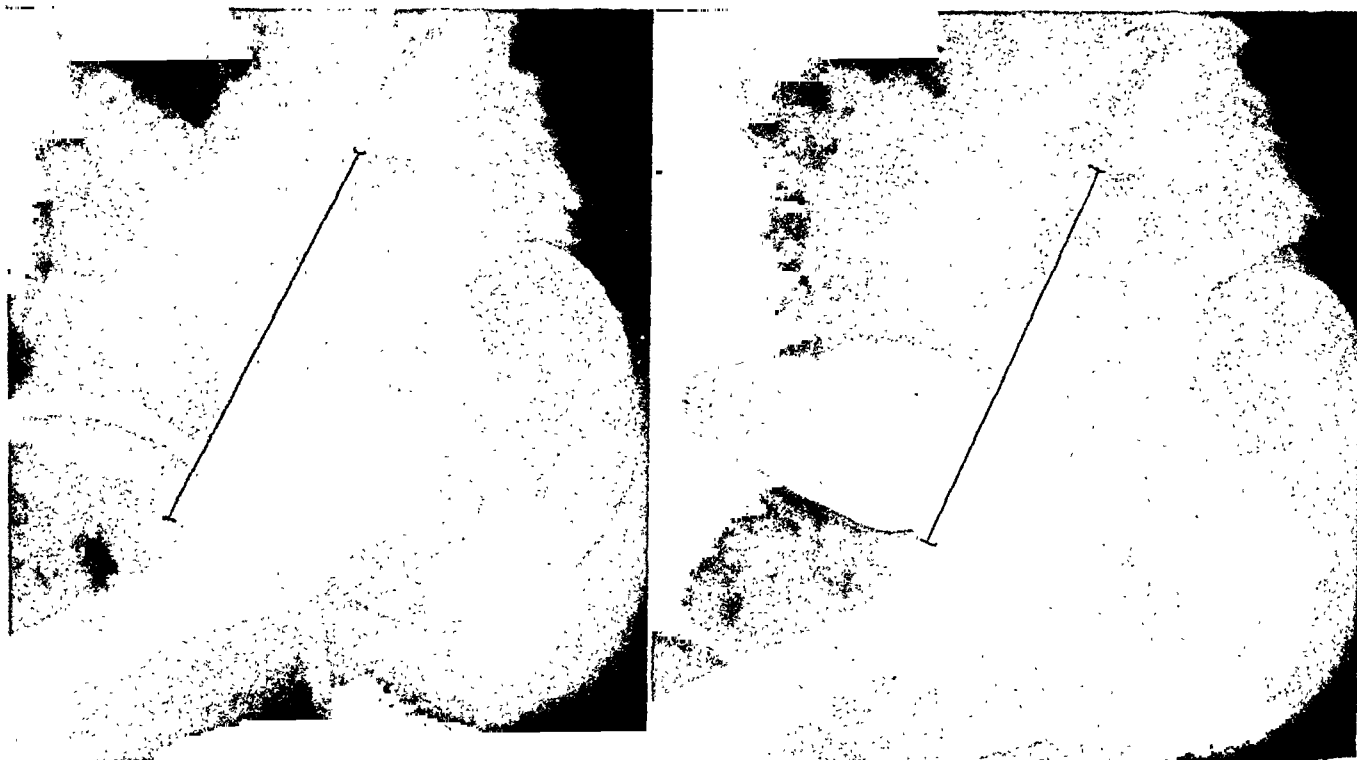


Fig. 6.—Vertex on pelvic floor. Roomy pelvis permits large pelvic portion of bladder. No significant obstruction demonstrated.

A. When the vertex was presenting, Fig. 4, pressure by the fetus on the pelvic portion was observed. The bladder seemed to follow the contour of the symphysis pubis. After catheterization, its pelvic location was unchanged, and the films still showed a similar relationship to the symphysis. The bladder did not cause significant obstruction.

B. When the breech presented, Fig. 5, the fetal parts seemed to fill the pelvis completely. Only the abdominal portion of the bladder was visualized and it offered no obstruction. Its effect on the aftercoming head was not demonstrated because of the obvious necessity of avoiding delay during delivery. Based on the facility with which fluid in the bladder seems to be displaced from the pelvis to the abdomen, it should ordinarily cause no obstruction.

IV. Late in labor, Figs. 6 and 7, with the presenting part near or on the pelvic floor, the bladder still retained a component in the pelvis. Again, some pressure by the fetus on this portion could be demonstrated. However, there was no obstruction to further descent or delivery. The application of low or outlet forceps, Fig. 8, revealed no impingement on the bladder. Moreover, slight traction resulted in further elevation of the fluid in the bladder. Roentgenograms showed some lengthening of the urethra during this phase.

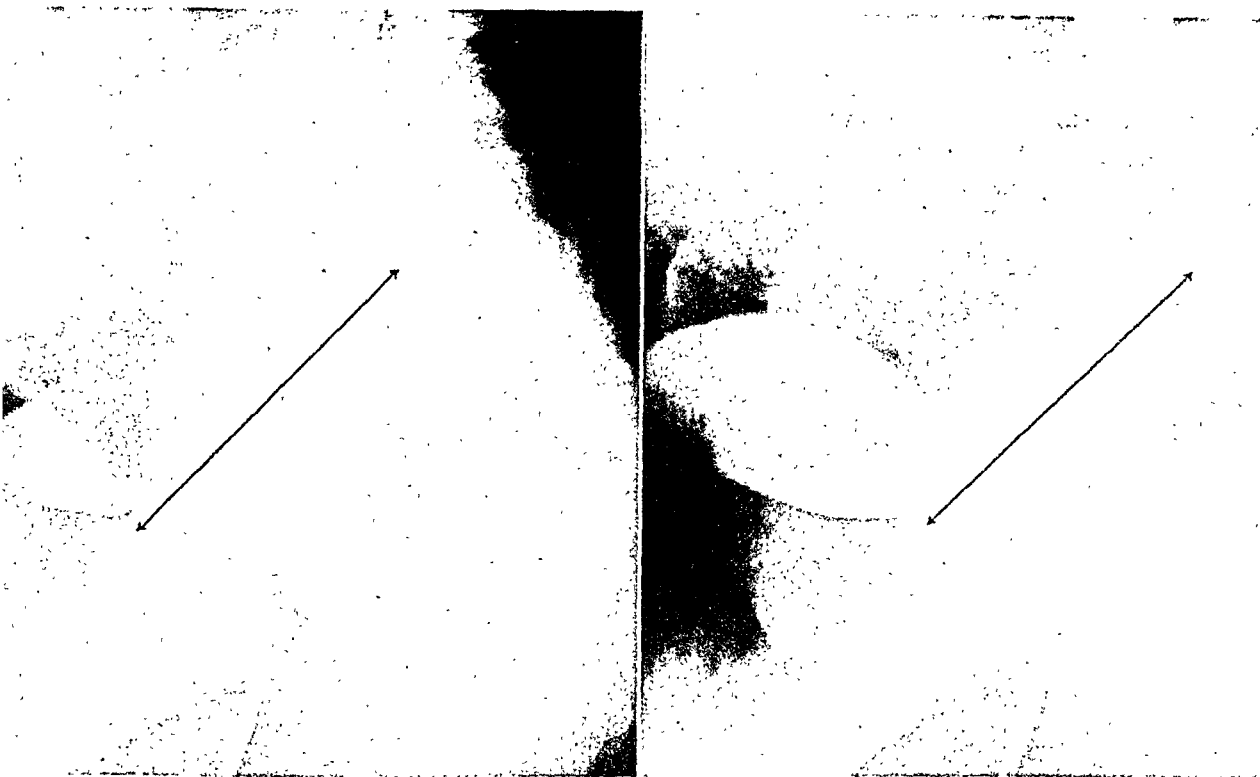


Fig. 4.—Vertex lies deep in pelvis. Distended bladder does not obstruct further progress and may diminish compression against symphysis.



Fig. 5.—Presenting breech fills pelvis. Distended bladder is wholly abdominal and causes no obstruction.



Fig. 8.—Vertex on pelvic floor. Forceps applied without bladder impingement. Slight traction results in elevation of bladder fluid to abdominal portion.



Fig. 9.

Fig. 9.—Head delivered. Soft parts fill the pelvis. Bladder wholly abdominal.



Fig. 10.

Fig. 10.—Fetus delivered. Uterus containing placenta partially fills pelvis. Bladder again has pelvic portion.

V. Following delivery of the head, Fig. 9, the bladder was situated above the pelvic brim because the soft parts completely filled the pelvis. Again some lengthening of the urethra was noted.

VI. After the fetus was delivered, Fig. 10, a portion of the bladder returned to the pelvis. Its location depended upon the extent to which the pelvis was filled. However, among the patients of this series, it offered no obstruction to the delivery of the placenta.



Fig. 7.—Pelvis less roomy; therefore, smaller pelvic component of bladder than in Fig. 6.

### Potential Injury From Compression (Cystometric Study)

The next aspect of this problem, then, was to determine the degree of compression to which the bladder was subjected. It was necessary to differentiate between the pressure caused by uterine contractions alone and that due to straining. Fortunately, these two components were so different, they were easily distinguished.

Cystometric studies performed in the usual manner represented the first attempt to measure these pressures. However, manometer levels could not be recorded until 100 to 150 c.c. were introduced into the bladder. Rose and Rollins,<sup>8</sup> and Muellner<sup>9</sup> demonstrated this bladder hypotonicity in pregnancy, and considered it to be similar to that of the upper part of the urinary tract.

In order to obtain readings with the bladder empty, a modified apparatus was used, Figs. 11 and 12. A Foley catheter with a rather loose bag, sufficiently large to hold 3 c.c. without stretching, was introduced into the bladder. Twelve cubic centimeters of water were injected into the bag and its outlet was connected to a manometer of small caliber. An equilibrium was established at approximately 50 cm., a gravity pressure adequate to maintain some distention of





Fig. 12.—Air cystogram. Foley bag is distended with contrast material to demonstrate its location during recordings.

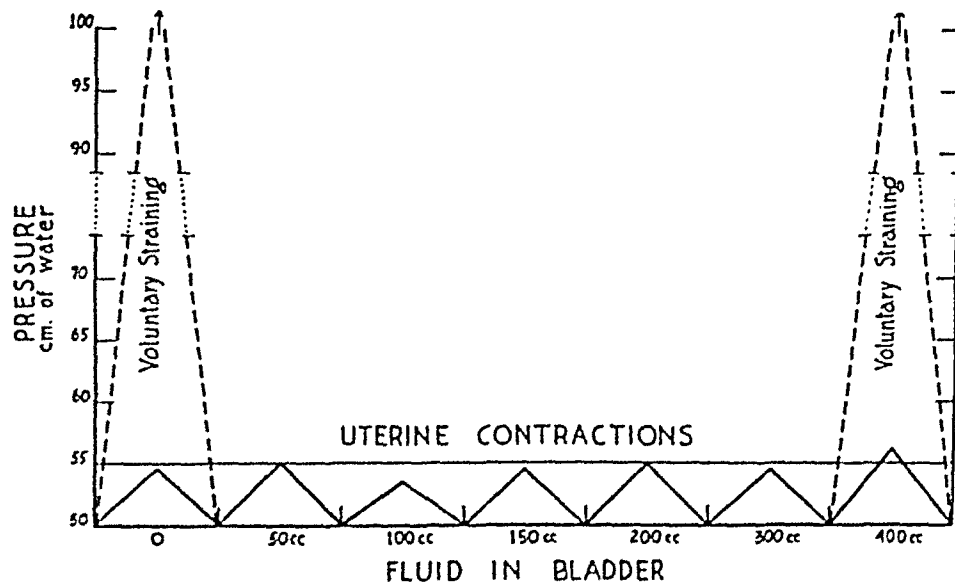


Fig. 13.—Average pressures resulting from uterine contractions and voluntary straining with varying amounts of fluid in bladder. (Late first or second stage of labor.)

the bag and to provide a base line for subsequent readings. Since 10 c.c. of fluid completely filled the manometer, forcible emptying of the bag caused it to overflow, a pressure of more than 50 cm. of water. When the patient was at rest, elevation of the manometer level was caused by pressure associated with uterine contraction and fetal descent.

Patients nearing the end of the first stage of labor were selected at random. They were given low spinal anesthesia or Demerol in order to control spontaneous expulsive efforts. Readings were taken during uterine contractions with the bladder empty, and distended with 50 to 400 c.c. of water. The effect of respiration was also noted. Finally, voluntary straining with the bladder empty and distended was permitted.

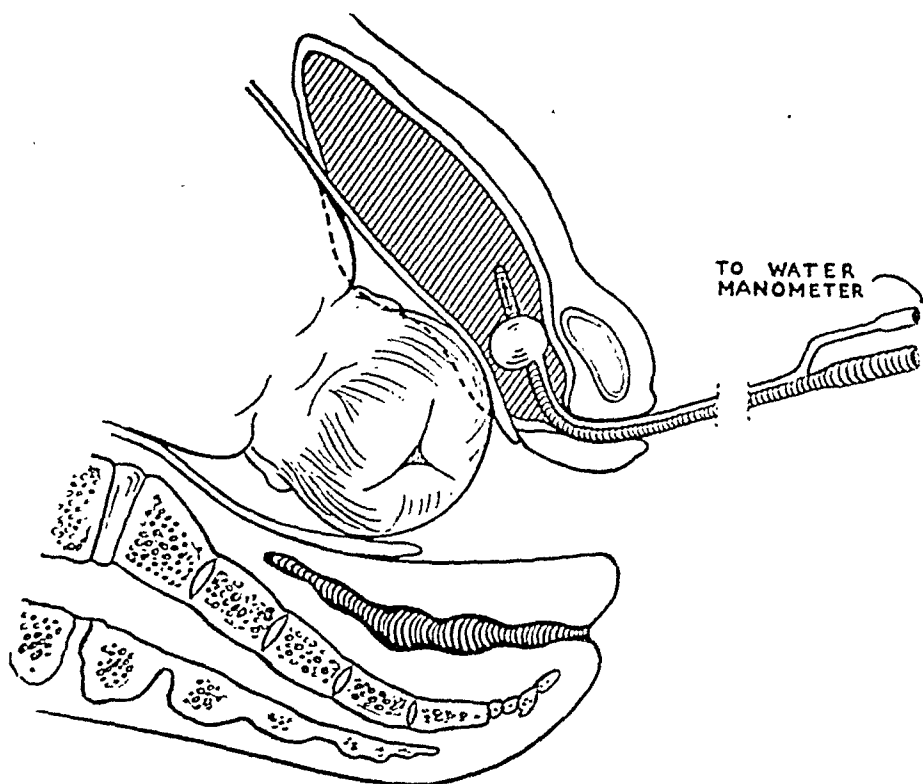


Fig. 11.—Drawing of Foley catheter apparatus for recording pressures.

## Results

Since the recordings with the usual cystometric technique and with the Foley bag were similar, they are reported together. During the height of a uterine contraction, the average rise was 5 cm. There were no significant differences when the bladder was empty or when it contained amounts up to 400 c.c. Prolonged straining always resulted in overflowing the manometer, and was equally effective with the bladder evacuated or distended. As noted above, this represented a pressure greater than 50 cm. of water.

The apparatus was sufficiently sensitive to record extravescial pressure changes of 1 cm. with ordinary respiration. It responded to suprapubic manual pressure by rising sharply. Moreover, the level rose about 2 cm. before the patient could identify the oncoming uterine contraction as a labor pain. (Perhaps this apparatus may be used to study the efficiency of uterine contractions.)

Fig. 13 presents average readings for varying degrees of bladder distention. A pressure of 5 cm. of water is equivalent to approximately 0.37 cm. of mercury.

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### Discussion

DR. CHARLES GALLOWAY, Chicago, Ill.—There is just a question that I would like to ask. It seems to me that you have the manometer connected to the wrong tube. I mean by that you have the manometer connected to the little rubber bulb which is a small confined amount of fluid down in the very lowest part of the bladder with even a possibility of the head reclining against it. May I ask if you tried putting the manometer on to the catheter to find out what the pressure really was inside the bladder. It seemed to me you recorded the pressure inside of this small confined amount of fluid rather than inside the vial.

DR. H. M. KIRSCHBAUM, Detroit, Mich.—I think this work is accurate and definite, but it brings up several very interesting things. I want to call attention to the fact that some twenty-five years ago when many deliveries were done in the home, practically speaking, I do not remember catheterizing many patients, when they had low forceps done. For the most part we did not do episiotomies in the home except occasionally, and if we did, we put three or four sutures in, but I want to call attention to the fact that the patients in the home were not getting any medications. We have an entirely different problem now in regard to the patient's realizing that her bladder is full.

I want to call attention to the fact that after low forceps or a spontaneous delivery, you are not certain that the patient will not have a postpartum hemorrhage. One of the treatments for that is massage of the uterus. If the bladder is full, and the patient is fairly obese, it may be rather difficult to catch hold of the fundus. Another method that has been advocated is the injection of Pituitrin through the abdominal wall. I would not want to do that if the bladder is full.

I would like to ask Dr. Kantor if in his studies he had made any observation on the amount of the postpartum catheterization that is necessary, whether it is more in patients who are allowed to deliver with the bladder full. I realize that the head is very low, and sometimes it is very difficult to catheterize the bladder before you can do a low forceps. Sometimes it is necessary to push the head up in order to insert the catheter, but I am anxious to have the bladder empty because I think in the postpartum era one of the causes of retroversion is the fact that the bladder is allowed to remain full.

This brings up one more point in connection with cystocele and episiotomy, which is always doubtful—where we do an episiotomy, do we prevent a cystocele?

This point is definite that in Detroit, since 96 per cent of patients were delivered in hospitals in 1947 compared to 20 per cent in 1922, there is much less postpartum gynecologic repair. This, one might suspect, is definitely associated with the fact that episiotomy is practically routine and the section rate is much higher.

DR. A. J. KOBAK, Chicago, Ill.—Occasionally I have seen where a large cystocele could cause the patient to have a dystocia. I wonder whether Dr. Kantor has made any studies where a large cystocele was present and what was the mechanism of the dystocia when it was present.

DR. KANTOR (Closing).—In answer to Dr. Galloway, in our original studies, the bladder portion of the catheter was connected to the manometer. Cystometric studies are usually performed in this manner. The results were exactly the same as those in which

### Comment

By means of the vaginal balloon technique, Murphy and Mengert<sup>10</sup> were able to measure the intra-abdominal pressures created in women by muscular effort alone. They state, "The average height to which the mercury column was raised . . . was 13.7 centimeters of mercury, a pressure of 2.65 pounds per square inch." With the Foley catheter technique, the straining pressures seemed to be similar whether the bladder was distended or empty. The pressure on the bladder caused by uterine contraction and fetal descent alone was insignificant and was not changed by catheterization. Moreover, a partially distended bladder may form a fluid cushion to minimize injury from compression against the symphysis. As the fetal parts filled the pelvis, the pressure associated with spontaneous descent or with forceps traction was adequate to displace urine into the abdominal portion of the bladder. Injury to the vesical supporting structures is due, therefore, to prolonged straining rather than to the pressure of uterine contraction, fetal descent, or to a distended bladder per se.

### Summary and Conclusions

1. The location of the bladder depends upon the degree to which the fetal parts fill the pelvis. It varies, therefore, with fetal descent and pelvic capacity. Its position, as determined by cystographic study, is not related to cervical dilatation.

2. The distended bladder can obstruct descent early in labor until the presenting part is well below the ischial spines. Evacuation is essential.

3. The bladder usually presents no obstruction when the presenting part is near or on the pelvic floor.

4. Routine catheterization is unnecessary prior to spontaneous delivery or to the application of low or outlet forceps.

5. Moderate bladder distention does not interfere with delivery of the shoulders or the body of the fetus.

6. Abdominal palpation of the bladder just prior to delivery may be physiologic. Unless hyperdistention is present, catheterization is not indicated.

7. Extravesical pressure due to uterine contraction and fetal descent averages 5 cm. of water. This does not vary with bladder content.

8. Straining pressures greater than 50 cm. of water were noted with the bladder empty or distended.

9. Pressure on the bladder can often be demonstrated even with the presenting part on the pelvic floor. Catheterization does not relieve this pressure since it does not change the location of the pelvic portion of the bladder.

We should like to express our gratitude to Dr. William F. Mengert for his kind assistance.

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## Original Communications

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### EVALUATION OF THE CYTOLOGIC TEST IN THE EARLY DIAGNOSIS OF CANCER

#### A Two-Year Survey of the Routine Use of the Smear Technique

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*(From the Strang Cancer Prevention Clinic of Memorial Hospital for the Treatment of  
Cancer and Allied Diseases)*

SINCE Papanicolaou and Traut<sup>1</sup> reported their observations on the diagnostic value of vaginal smears in carcinoma of the uterus, this method has been widely accepted. This technique was first introduced by L'Esperance<sup>2</sup> for screening in cancer prevention clinics. The diagnosis of this method is based on the principle that malignant cells, due to their high proliferative activity, exfoliate into the body fluids long before the lesion is recognized clinically. An appropriate term for this study is "exfoliative cytology."<sup>3</sup> Meigs et al.,<sup>4</sup> Ayre and Graham,<sup>5</sup> Jones et al.,<sup>6</sup> and Fremont-Smith<sup>7</sup> have conclusively confirmed the value of exfoliative cytology in the diagnosis of cancer of the female genital tract. Gates and Warren<sup>8</sup> have pointed out the different applications of the vaginal smear method in diagnosis of uterine cancer: 1. for the study of obscure conditions, such as borderline lesions of uncertain significance and those that cannot be diagnosed by the usual methods; 2. for diagnosis in selected cases; 3. for determination of the sensitivity to irradiation of cancer of the uterus in individual cases; 4. As a routine test in general physical examinations; 5. as an adjunct to biopsy in diagnosis of gynecologic cases generally.

In addition to the vaginal fluid, this method may be used with various types of body fluids which contain the exfoliated cells. The fluids may be bronchial secretions, gastric contents, urine sediment, sputum, and others. The recent reports of Papanicolaou, Marshall, and Cooper,<sup>9</sup> Herbut and Clerf,<sup>10</sup> Woolner and McDonald,<sup>11</sup> Hunter and Richardson,<sup>12</sup> and Campbell and Grimm<sup>13</sup> are very encouraging.

#### Material and Method

The purpose of this paper is to evaluate the routine use of the cytologic test in the diagnosis of early cancer of the uterus from data obtained in 1946 and 1947, in the Strang Clinic. Approximately 8,000 asymptomatic women had vaginal and cervical smears for the detection of early cancer of the genital tract. In every case a minimum of two smears were taken, a vaginal and a cervical. The vaginal fluid was aspirated with a glass pipette attached to a rubber bulb after it had been carefully placed in the posterior fornix. No lubricants were

the Foley bag was connected to the manometer. Since pressure on fluid is distributed equally and undiminished in all directions, any increase in intravesical pressure is reflected by a similar increase on the Foley bag.

Answering Dr. Kirschbaum, regarding abdominal pressure during breech delivery, it is often difficult to gauge the degree of manual pressure which is being applied. Its use has been discouragd by many competent obstetricians.

Regarding postpartum massage, we do not advocate delivery of all patients in the face of a distended bladder. During this study, hyperdistention was permitted in order to demonstrate the physiology of the bladder during labor. We believe that catheterization of the bladder is not essential prior to spontaneous or outlet forceps delivery. Moreover, the retention of small amounts of urine may be physiologic at this time. On the other hand, when the presenting part is fairly high in the pelvis, catheterization to relieve distention may become mandatory. At this phase, distention of the bladder may interfere with the normal progress of labor.

Regarding the prevention of cystocele by liberal use of episiotomy, may I refer to an article by Dr. Mengert published several years ago in which the supports of the uterus and vagina were studied in detail. Although we do see fewer patients who require vaginal plastic procedures, I do not think episiotomy in itself is the whole story.

In the presence of some degree of bony dystocia, the fetus may develop a large caput so that the presenting part may appear to be on the perineal floor. Since the head is usually fairly high in the pelvis, catheterization is necessary prior to delivery.

ate suction the fluid is obtained. Frequently, in elderly postmenopausal women or those with atrophic vaginitis, the vaginal and cervical secretions are scanty. In such cases, the procedure should be repeated until adequate material is obtained for staining, for not too infrequent false negative reports may be the result of this neglect. If the fluid remains scanty, washings of the vagina may be used. This is done with a solution of equal parts of saline and 10 per cent alcohol. The washings thus obtained are centrifuged, and a portion of the sediment is placed on an albumin-coated slide and fixed as already described. The remainder of the sediment can be preserved for additional smears if needed. All smears are prepared and stained according to the technique of Papanicolaou.<sup>14</sup>

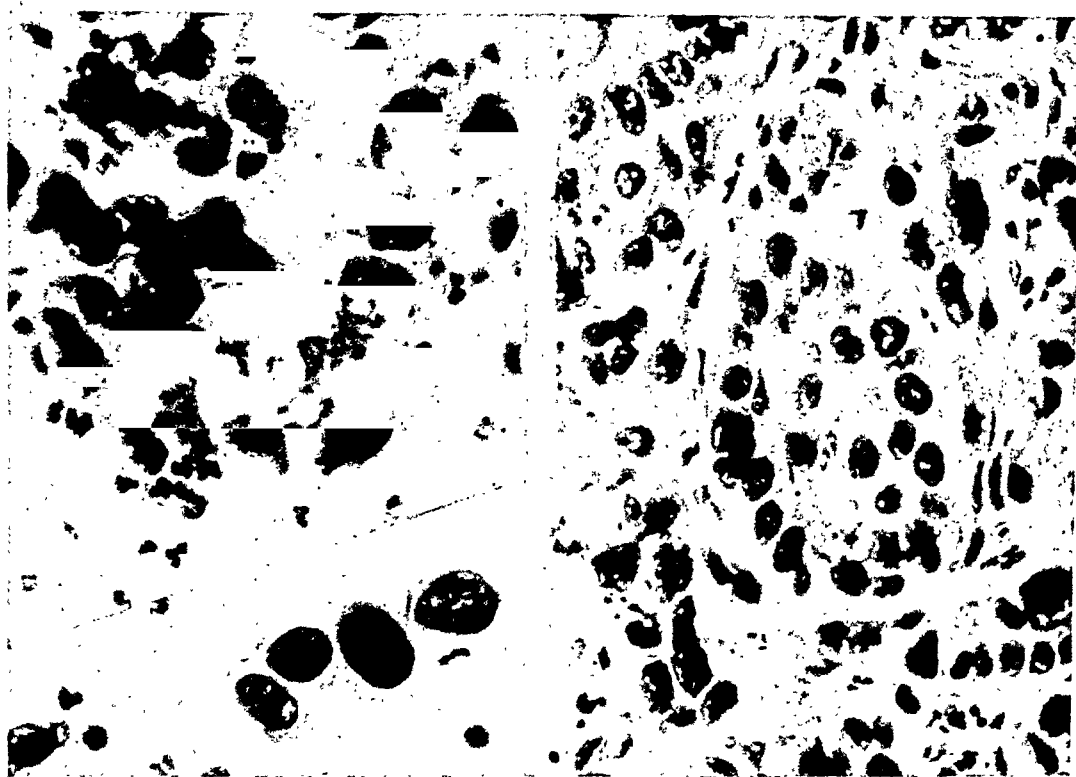


Fig. 4.—Cluster of malignant cells showing overcrowding and loss of pattern. Case of squamous-cell carcinoma of the cervix, biopsy included. (X540)

In our series, the diagnosis of malignancy in some instances was based on the findings from the cervical smear while the corresponding vaginal smear was negative; therefore, it is advisable to take adequate vaginal and cervical material from each patient. Vaginal aspiration alone is not the best procedure to follow for optimum results. The menstrual history of the patient at the time when the smears are taken, a history of hormone therapy, irradiation, or pelvic surgery are important for the evaluation of atypical cells. Smears should be examined under high as well as low magnification. Isolated suspicious or positive cells may be easily overlooked if only low power is used.

The time required to examine a slide adequately varies with the experience of the examiner. Screening of slides can be done by trained personnel, leaving only suspicious and positive slides to the cytologist. With proper experience one may examine, on an average, four to six cases per hour.

used in this procedure. The fluid was then spread on a slide and fixed immediately in equal parts of 95 per cent alcohol and ether for at least one hour. The cervical smear was obtained by gently swabbing the external os with a cotton swab. The fluid on the swab was spread on a slide and fixed in the same manner.

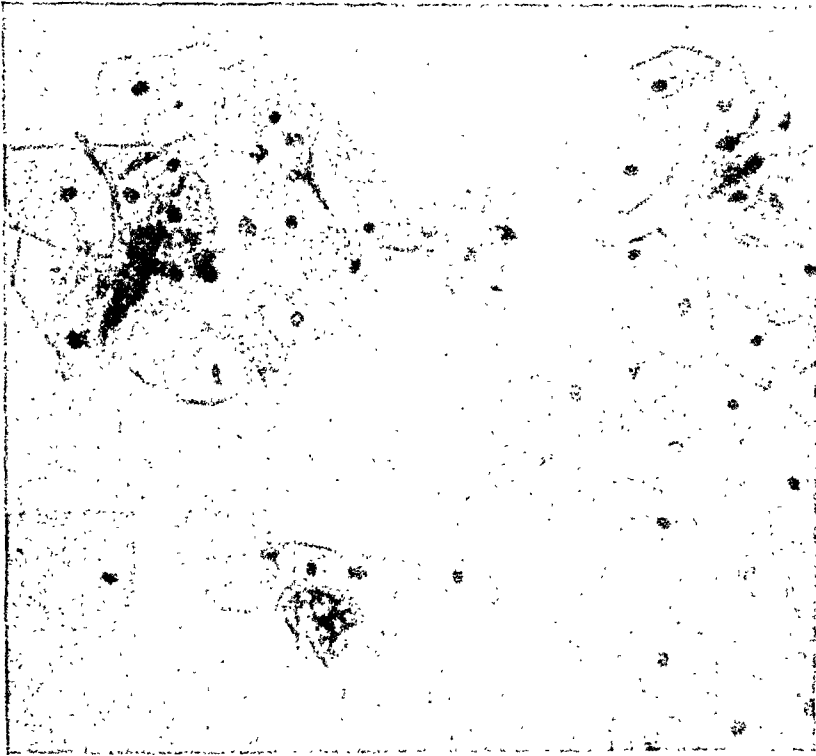


Fig. 1.—Vaginal smear showing normal superficial epithelial cells. ( $\times 510$ )

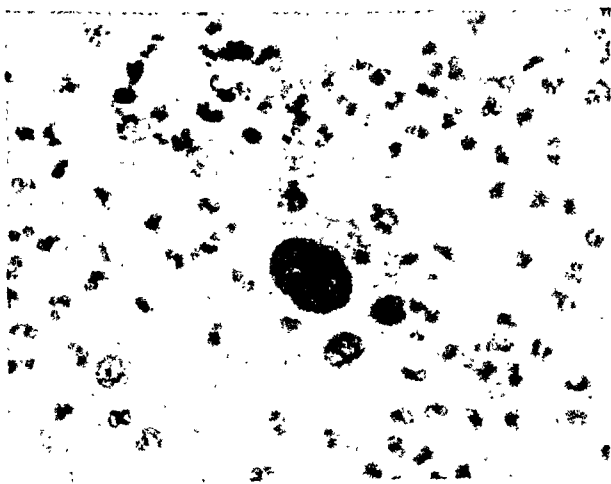


Fig. 2.

Fig. 2.—Isolated malignant cell. ( $\times 540$ )

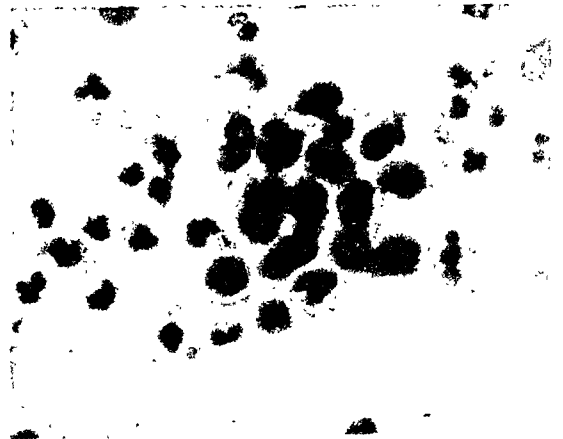


Fig. 3.

Fig. 3.—Cluster of malignant cells. ( $\times 540$ )

Fundal carcinoma can be ruled out with more accuracy by using an endometrial aspiration in addition to the vaginal smear. This is performed with a sterile infant laryngeal cannula introduced beyond the internal os; with moder-



seen in metaplasia. "Tadpole-shaped" cells and hypercornification are seen in malignant as well as in nonmalignant lesions; therefore, these features are not to be considered specific for malignancy.

Classification

The specimens are reported in one of five classes according to Papanicolaou. Class I and Class II are negative, Class III is suspicious, and Class IV and Class V are positive. The evaluation of each of the five classes is given in Table I.

TABLE I. CLASSIFICATION OF REPORTS ON SMEARS AS APPLIED TO THE DIAGNOSIS OF MALIGNANT NEOPLASMS, AFTER PAPANICOLAOU

CLASS		
I	NEGATIVE	Absence of atypical or abnormal cells
II		Atypical cells present but without abnormal features
III		Cells with abnormal features suggestive but not conclusive for malignancy
IV		
V		Cells and cell cluster conclusive for malignancy

Smears which are classified as Class I require no repeat until the next visit of the patient. Patients under forty-five have pelvic examinations once a year. Patients over forty-five have pelvic examinations every six months. Those classified as Class II require repeat of smear within three months, in order to check the persistence of atypical cells. In this group, we include nonmalignant lesions, such as vaginitis, cervicitis, polyps, leucoplakia, etc. (Fig. 7). Class III and Class IV require immediate repeat. Investigation by other diagnostic methods such as biopsy or curettage is strongly advised. Class V includes cases in which the positive diagnosis appears to be well established, but these are also subjected to further exploration by other diagnostic methods.

Laboratory and Clinical Data

During 1946 and 1947, 7,777 asymptomatic women were examined in our clinic, 4,160 in 1946 and 3,617 in 1947. Among these, twenty-two carcinomas of the female genital tract were detected. Twenty-one of these twenty-two cases were proved to be positive first by smear and then by biopsies. This is shown in Table II. These findings give us approximately one positive case per 354 women examined. The laboratory and clinical data are also shown in Table II.

### Criteria of Malignant Cells

The correct diagnosis of a smear requires a thorough acquaintance with the normal cytology of the material being studied (Fig. 1). One cannot over-emphasize that the accuracy and dependability of the test depend upon a correct interpretation of the findings. The criteria of the malignant cells as seen in the vaginal smear have been described in detail.<sup>8, 15</sup> The most significant of these are: 1. the tendency of the nucleus to be unusually large in proportion to the cytoplasm; and 2. the nuclear richness in chromatin content, i.e., hyperchromatism, also fragmentation and irregularities of the nucleus with thickening of the nuclear membrane and prominence of the nucleoli. Aberrant cells suggestive of carcinoma may be found either singly or in clusters (Figs. 2 and 3). The loss of pattern and overcrowding of cells is of particular importance in the cluster forms (Figs. 4 and 5). These aberrations are characteristic of epidermoid carcinoma of the cervix as well as adenocarcinoma of the fundus. In adenocarcinoma an abnormal vacuolization of the cytoplasm is seen, in which the vacuoles are frequently infiltrated by leucocytes (Fig. 6). Vacuolization of the cytoplasm in cervical cells has no significance for malignancy. Thickening of the nuclear membrane is quite often seen in cancer cells, but this is not specific for malignancy because it is also seen with chronic inflammation and irritation.

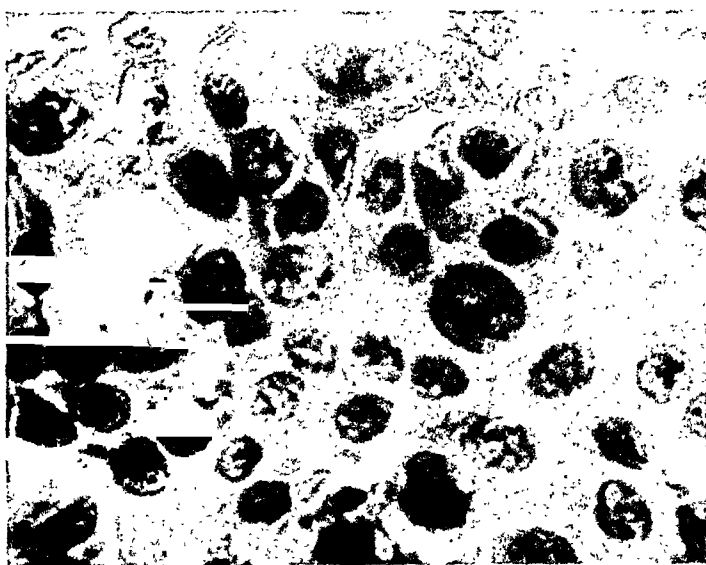


Fig. 5.—Vaginal smear of a case of intraepithelial carcinoma of the cervix. (X540)

There are certain features which are not pathognomonic of malignancy, but may add supporting evidence to suspicious findings. These may be an excessive number of degenerated cells or the presence of many active histiocytes. However, a histiocytic reaction may also be found in inflammation and normally in the postmenstrual period, or following coitus; however, in the absence of these, their presence in excess is suggestive of a malignant process. Bleeding which cannot be attributed to known causes may also be considered suspicious for malignancy.

With the present state of our knowledge of exfoliative cytology, we have no criteria which could be applied in the diagnosis of precancerous lesions. Epidermization is considered by some as precancerous. Atypical cells are often

TABLE II. LABORATORY AND CLINICAL DATA IN 21 CASES OF CARCINOMA OF THE GENITAL TRACT PROVED BY VAGINAL SMEARS AND CONFIRMED BY BIOPSIES

CHART NUMBER	AGE	FINDINGS ON FIRST GYN. EXAM	DATE AND CLASSIFICATION OF SMEARS	FURTHER VAGINAL SMEARS	BIOPSY	TREATMENT AND CLINICAL COURSE
2,220 C. H.	42	Cervical erosion	12/11/46 IV	3/20/47 IV	5/14/47 Intraepithelial ca.	Hysterectomy
2,847 D. M.	42	None	8/ 8/46 IV	None	10/19/46 Epidermoid ca. Grade II	No follow up
4,850 C. R.	35	Cervical erosion	1/ 2/46 IV	2/14/46 IV	1/29/46 Intraepithelial ca.	Hysterectomy
4,999 M. J.	40	Chronic cervicitis	1/23/46 III	10/31/46 III	1/23/46 Intraepithelial ca.	Hysterectomy
5,409 S. R.	47	Granular erosion	1/11/46 IV	None	1/11/46 Epidermoid ca. Grade II	Irradiation Subsequent smears negative Irradiation
5,465 E. S.	45	None	1/15/46 III	None	1/23/46 Intraepithelial ca.	No follow up
5,499 A. S.	49	Cervical erosion	8/ 8/47 IV	None	8/ 8/47 Epidermoid ca. Grade II	No follow up
5,500 G. B.	48	Cervical erosion	1/18/46 IV	2/ 1/46 2/26/46 IV	1/26/46 Intraepithelial ca.	No follow up
6,516 J. F.	45	Cervical erosion	4/ 3/46 III	1/28/47 III	4/ 4/46 4/17/46 Intraepithelial ca.	No follow up
6,720 H. H.	40	Cervical erosion	4/16/46 III	11/20/47 III 12/12/47 IV	4/16/46 12/23/47 Chronic cervicitis	Hysterectomy Epidermoid ca. Grade III.

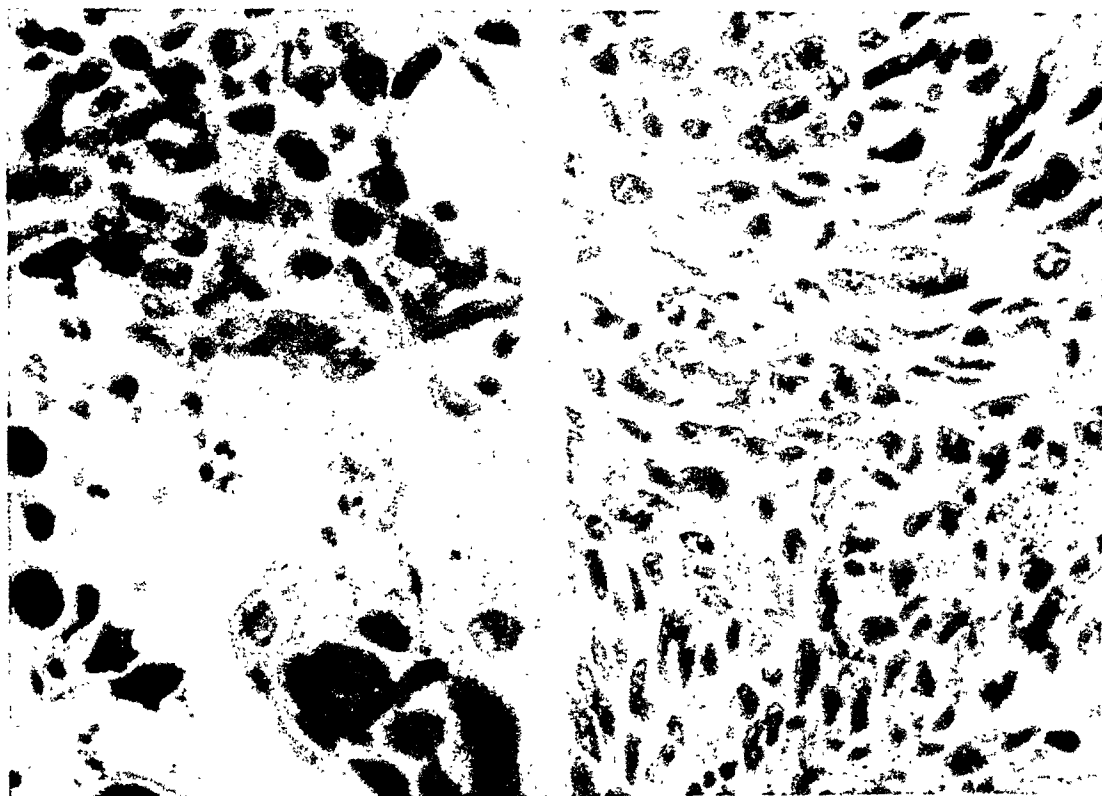


Fig. 6.—Vaginal smear and biopsy of a case of adenocarcinoma of the uterus. ( $\times 540$ )

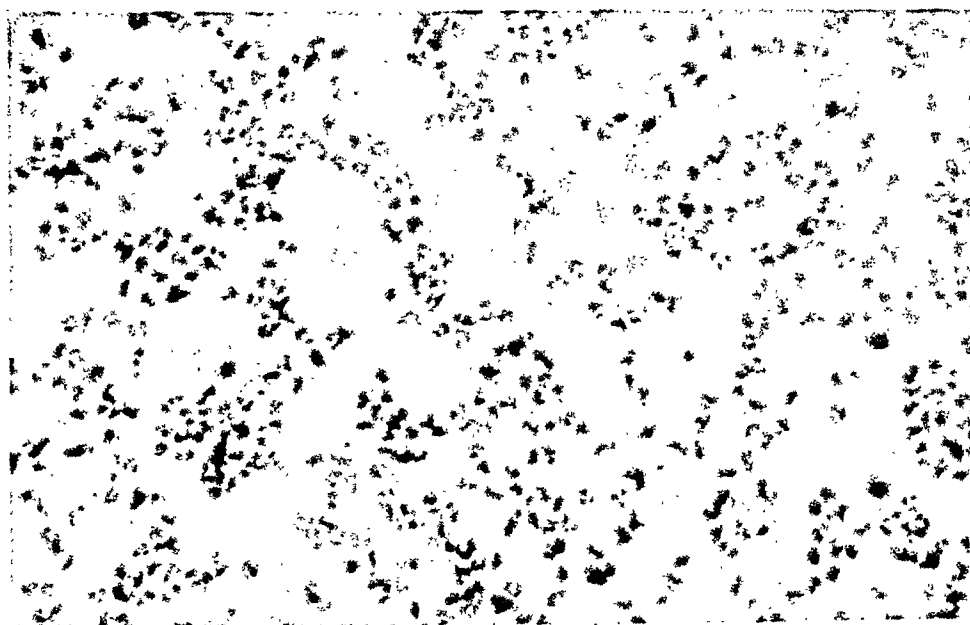


Fig. 7.—Smear showing a case of infection, Class II. ( $\times 540$ )

Among these 21 cases the first smear was reported as Class III in 12 cases (57 per cent) and Class IV in 9 cases (43 per cent). On subsequent smears, some of the original Class III were reclassified as IV and one as V. On reviewing the clinical data it is of interest to see that in three cases (14 per cent) the findings were negative on physical examination, while the remaining eighteen cases (86 per cent) showed some evidence of pathology. On further exploration, nineteen cases (90 per cent) proved to be carcinoma of the cervix, one case (5 per cent) adenocarcinoma of the fundus, and 1 case (5 per cent) a metastatic spindle-cell sarcoma. Of the cervical carcinomas, 12 cases (63 per cent) revealed intraepithelial carcinoma, i.e., carcinoma in situ, five cases (26 per cent) epidermoid carcinoma Grade II, and two cases (11 per cent) epidermoid carcinoma Grade III.

TABLE III. TYPE AND PERCENTAGE OF CASES IN TABLE II.

TYPE	NUMBER	PER CENT
Intraepithelial epidermoid carcinoma	12	57
Epidermoid carcinoma Grade II	5	23
Epidermoid carcinoma Grade III	2	10
Adenocarcinoma, fundus	1	5
Metastatic spindle-cell sarcoma, uterus	1	5

TABLE IV. AGE INCIDENCE OF CASES IN TABLE II.

AGE (YEARS)	NUMBER	PER CENT
35 to 39	4	19
40 to 49	13	62
50 to 59	3	14
61	1	5

There are two additional cases which bring out the problems of false positive and negative reports. Case No. 13,928 (M. H.) reported Class III on one occasion and Class IV on four subsequent examinations, has not as yet been confirmed by biopsy. This case is not considered closed, and further exploration may confirm or disprove our diagnosis. Case No. 8,716 (H. D.) had three negative reports on smears, but biopsy was reported as positive for intraepithelial carcinoma. Following a total hysterectomy, the surgical specimen was reported as adenosis of the cervix without cancer.

### Summary

1. In 1946 and 1947, in the Strang Clinic of Memorial Hospital, approximately 8,000 asymptomatic women had routine vaginal and cervical smears for the detection of cancer of the genital tract. The method as applied in the clinic is discussed.

2. The significant features of the criteria of malignancy as seen in cytologic studies are evaluated.

3. A classification of the findings on smears as applied to the diagnosis of malignant neoplasm is presented.

4. Our findings result in twenty-two positive cases of carcinoma of the female genital tract, which is approximately one case per 354 asymptomatic women examined. Twenty-one cases were substantiated by biopsies. The re-

7,676 F. S.	44	Cervical polyp and erosion	6/13/46 IV	None	6/11/46 6/24/46 Intraepithelial ca. 7/13/46 Epidermoid ca. Grade III 3/ 5/47 Adenocarcinoma, fundus 8/13/46 9/ 2/46 1/16/46 Intraepithelial ca. 3/22/47 Spindle-cell sarcoma	Hysterectomy
8,020 E. R.	49	Cervical erosion	6/20/46 III	7/12/46 IV		No follow up
8,707 J. K.	56	Vaginal bleeding	8/13/46 III	None		Hysterectomy
8,716 H. D.	40	Cervical erosion	8/13/46 III	None		Hysterectomy
9,085 R. M.	61	Cervical polyp	9/13/46 III	12/ 6/46 III		Operation for retro- peritoneal tumor, metastases uterus
10,412 M. R.	44	Cervical erosion	10/25/46 IV	None	11/26/46	No follow up
11,380 D. B.	51	Laceration of cervix	1/21/47 III	None	Epidermoid ca. Grade II 1/22/47	No follow up
11,739 L. A.	39	Cervical erosion	2/13/47 III	11/26/47 V	Epidermoid ca. Grade II 11/11/47 11/26/47	No follow up
12,086 M. C.	37	None	3/ 6/47 III	3/24/47 IV	Intraepithelial ca. 3/ 7/47 Intraepithelial ca. 3/24/47	No follow up
12,125 L. N.	50	Laceration of cervix	3/26/47 IV	None	Suspicious 4/12/47	Hysterectomy
16,120 M. J.	35	Cervical erosion	12/16/47 III	12/22/47 IV	Intraepithelial ca. 12/16/47 Intraepithelial ca.	No follow up

## FURFURYL TRIMETHYL AMMONIUM IODIDE (FTAI) FOR POSTOPERATIVE URINARY RETENTION

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URINARY retention and difficulty in initiating micturition have been frequent complications following abdominal and vaginal operations. The associated discomfort and disability have at times resulted in prolonged hospitalization. Although many methods of treatment have been used, including indwelling catheters, periodic catheterization with and without bladder instillations, hot baths, tincture of hyoseyamus and other antispasmodics, the problem of postoperative urinary retention has continued to be a major one.

The urinary bladder<sup>1</sup> is supplied by both the parasympathetic and sympathetic nervous systems (Fig. 1); their fibers convey sensations of vesical pain and the degree of muscular distention. The sympathetic efferent nerves furnish inhibitory fibers to the detrusor muscle and motor fibers to the trigone, internal sphincter, and smooth muscle of proximal portion of the urethra. These sympathetic fibers arise from the lumbar sympathetic segments from L-1 to 2, running to the hypogastric ganglion; their postganglionic fibers enter into the formation of the vesical plexus. The parasympathetic efferent nerves supply motor fibers to the detrusor muscle and inhibitory fibers to the internal sphincter arising from S-2 and 3. The postganglionic fibers arise from cells within the bladder wall. Division of the sympathetic fibers does not interfere with micturition whereas section of the parasympathetic fibers causes paralysis of the bladder. The parasympathetic motor fibers convey impulses for emptying of the urinary bladder. Therefore, the most important pathway for contraction of the bladder is the parasympathetic nervous system. A new parasympathomimetic drug, furfuryl trimethyl ammonium iodide, was used in an attempt to reduce and prevent postoperative vesical distention in gynecological surgery.

Furfuryl trimethyl ammonium iodide (FTAI), commercially known as Furmethide,<sup>6</sup> is closely related to a large group of parasympathomimetic drugs such as acetylcholine, Meeholyl, Doryl, muscarine, pilocarpine, Prostigmine, and physostigmine (Fig. 2). The general close relationship is apparent after comparison of their structural formulas. The actions of FTAI have been studied in animals by Fellows and Livingston,<sup>2</sup> and later in man by Myerson,<sup>3</sup> Beaser,<sup>4</sup> and Bondy,<sup>5</sup> and their co-workers. The subcutaneous injection of 3 mg. of FTAI results, after five minutes, in a diffuse flush, diaphoresis, profuse salivation, and slight tachycardia. Simultaneously there is a desire to void. Cystometric determinations reveal a rise in bladder tonus. Roentgen examination of the ureters and bladder with opaque material demonstrates active contractions after the administration of FTAI. Larger doses result in a transient decrease in blood pressure and a slight elevation in venous pressure. No instances of heart block

\*We hereby acknowledge our gratitude to the Smith, Kline and French Laboratories for furnishing us with our supply of furfuryl trimethyl ammonium iodide (Furmethide).

maining case continues positive smears in spite of repeated negative cervical biopsies. One case showed negative smears prior to the positive cervical biopsy although the surgically removed uterus showed only adenosis.

### Conclusion

The results obtained in 1946 and 1947 with the routine use of the cytologic test in the detection of cancer of the female genital tract have been very encouraging. Other body fluids, namely, sputum, gastric contents, urine sediment, prostatic fluid, and rectal mucus are now being subjected to cytologic studies in our clinic, as a screening method for the early detection of cancer.

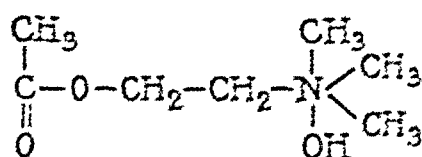
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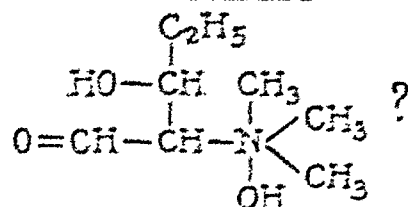


more convenient to determine the time of voiding and other effects of the drug. Two to three minutes after the injection, a diffuse flush of the face was observed which was followed by generalized diaphoresis and moderate salivation.

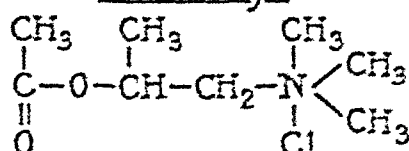
### Acetylcholine



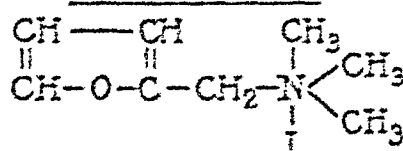
### Muscarine



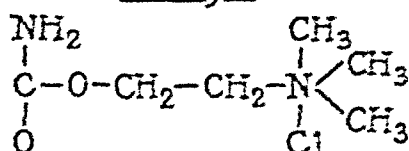
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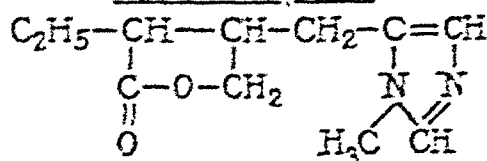
### Furmethide



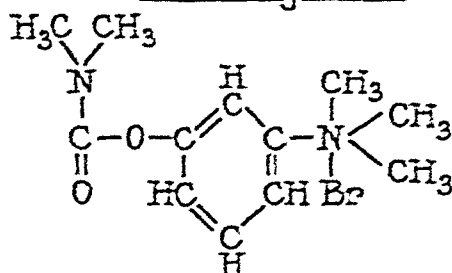
### Doryl



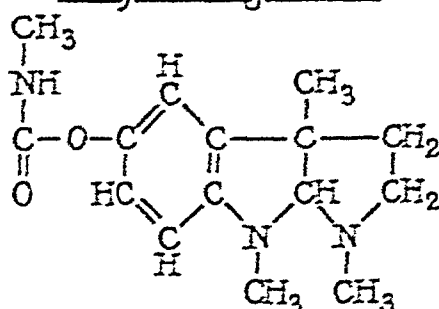
### Pilocarpine



### Prostigmine



### Physostigmine



## Parasympathomimetic Compounds

Fig. 2.

A transient reduction in blood pressure of 10 to 20 mm. was noted in one patient. Slight tachycardia was frequent. After five minutes there was pain over the bladder area; this was followed by an intense desire to void. Micturition occurred in from five to twenty minutes after parenteral administration.

have been reported. Several patients have complained of mild and transient disturbance in visual accommodation; this has been reported by Myerson and Thau.<sup>6</sup> Doses as large as 10 mg. subcutaneously rarely produce gastrointestinal symptoms. Roentgenological examinations of the stomach, colon, and gall bladder revealed no apparent change in motility. Hysterosalpingograms reveal no contractions of uterine or tubal musculature. Oral doses as large as 30 mg.

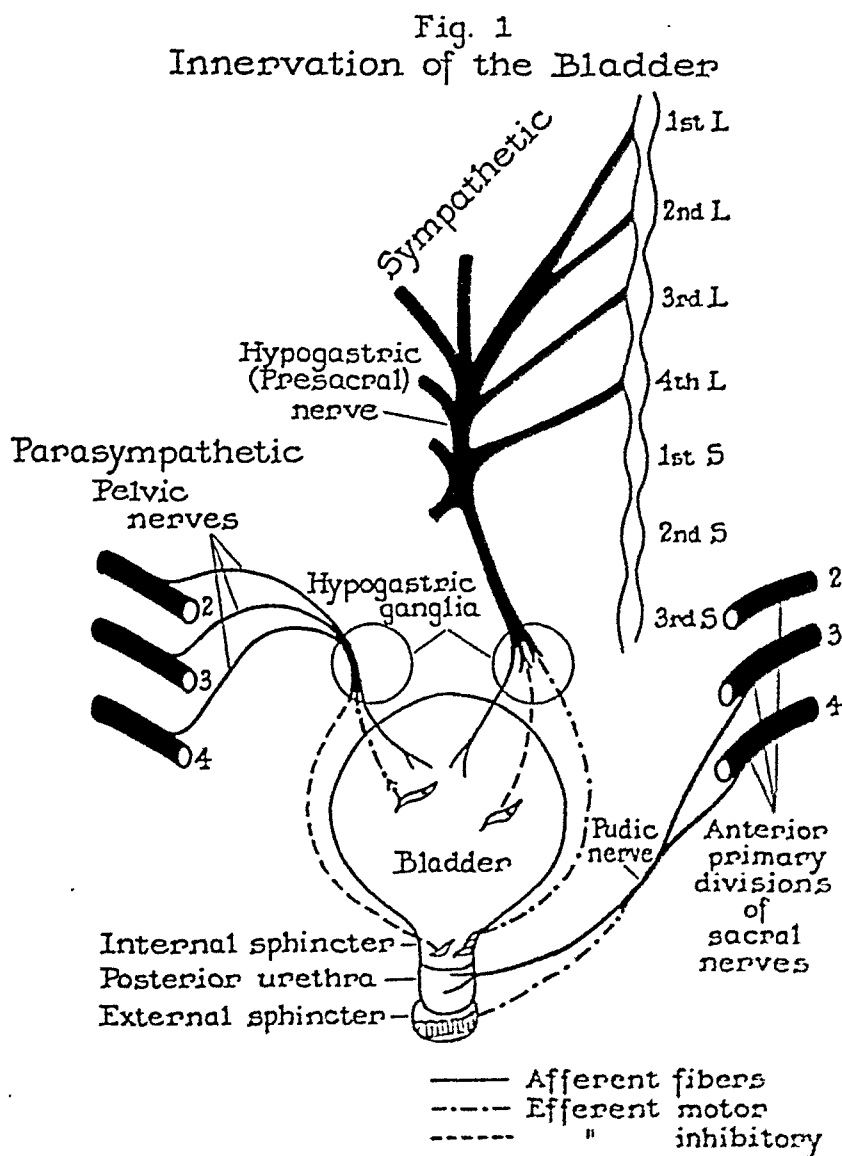


Fig. 1.—Innervation of the bladder. (After Learmouth.)

cause only perspiration and an increase in vesical tone. FTAI was found to exert less action on the cardiovascular system and bronchi than Mechohyl, and less action on the gastrointestinal tract than Doryl and Prostigmine. However, its effect on the bladder seems to be stronger and more constant than with any of the other drugs. Moreover, FTAI may be administered orally; this results in a slow gradual summation in its effect, simulating the normal desire for micturition.

At the beginning of our investigation, patients received Furmethide subcutaneously in doses of 2.5 to 3 mg. The use of the parenteral route made it

void and was catheterized every eight hours, yielding from 200 to 600 c.c. (Fig. 3). At the end of the second day patient began to void small amounts from 50 to 250 c.c. Large residuals, as high as 700 c.c., continued until the seventh postoperative day, at which time Furmethide was administered orally in doses of 10 mg. three daily. Within one day spontaneous normal voiding began and residuals dropped to 25 c.c. The use of Furmethide was discontinued after three days.

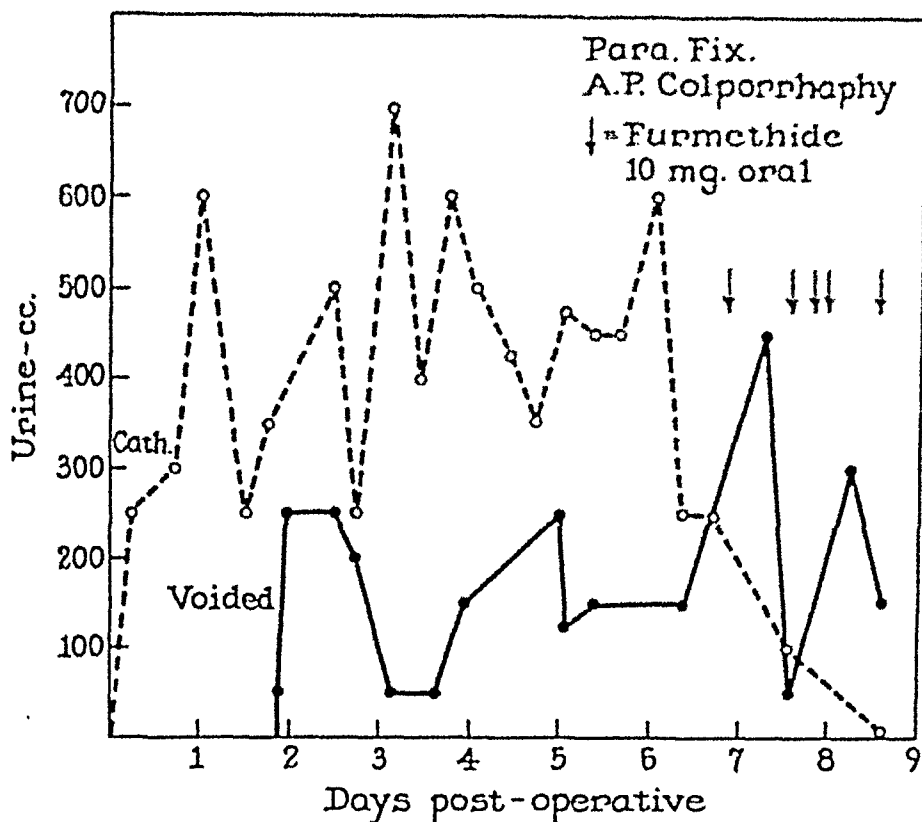


Fig. 3.

CASE 2.—B. A. (576858), a 56-year-old white married woman, suffered from cystoectocoele and prolapse of the uterus. Parametrial fixation and anterior and posterior colporrhaphy were performed on Feb. 19, 1948. For six days after these operations no voiding occurred (Fig. 4). Catheterization every six hours yielded from 200 to 700 c.c. On the seventh day patient voided 50 to 250 c.c. but continued to have residuals of over 300 c.c. On the eighth day Furmethide was started; residuals immediately decreased to 50 c.c. with voiding of 400 c.c. Furmethide was continued for two days. Spontaneous voidings continued as long as the patient remained in the hospital.

The authors are indebted to Dr. Joseph A. Gaines for permission to use his records of this case.

CASE 3.—R. F. (574984), a woman, aged 50 years, was admitted for urinary stress incontinence and cystoectocoele. On Jan. 6, 1948, urethroplasty, and anterior and posterior colporrhaphy were performed. For five days following operation no voiding occurred and periodic catheterization revealed from 200 to 900 c.c. of urine (Fig. 5). On the sixth post-operative day the use of Furmethide was started; spontaneous urination resulted, with residuals below 100 c.c. and voiding continued with amounts up to 400 c.c.

Because of the collateral effects produced by injection of the drug, and in order to simplify the administration, oral therapy was studied. Ten to twenty mg. were given initially and continued at 10 mg. three times a day until satisfactory spontaneous voiding occurred. Usually the drug was continued for two to four days; with the oral administration, slight sweating and salivation occurred in fifteen to thirty minutes and a desire to void was present in thirty to sixty minutes. Micturition usually resulted one hour after the oral dose. The side effects were absent or mild. Salivation and diaphoresis were more easily tolerated when the patient was warned of such possible effects. Several patients received the drug orally for seven to ten days in order to note cumulative toxicity; none was observed. Prolonged administration was used to accumulate data as to the degree of vesical emptying and amount of residual. In order to test this drug further, Furmethide was administered to patients with prolonged postoperative urinary retention varying from three to ten days in duration. After such protracted periods of catheterization, spontaneous micturition began within twenty-four to thirty-six hours after commencement of FTAI therapy.

These satisfactory results encouraged the authors to use the drug earlier during the postoperative period. More recently, as soon as the patient has reacted from anesthesia, Furmethide was begun in order to prevent the need for catheterization. At present the routine use of the drug commences with the administration of 10 mg. of Furmethide three times a day as soon as fluids are tolerated. The drug is usually given four to five hours after operation to initiate micturition at about six hours. If the oral use is contraindicated, 2.5 to 3 mg. of Furmethide may be given subcutaneously every eight hours. The presence of vaginal packings does not contraindicate the use of the drug unless actual compression of the urethra has been produced. If definite obstruction of the urethra or neck of the bladder is found, Furmethide should not be used.

In this preliminary report we are analyzing the data obtained from one hundred patients (Table I) who received Furmethide after various gynecological operations. In this group there were two failures, which will be described in detail.

TABLE I. OPERATIVE CASES TREATED WITH FTAI

<i>Abdominal Operations</i>		59
Total hysterectomy	26	
Subtotal hysterectomy	17	
Adnexal resections	10	
Myomectomy	2	
Laparotomy	4	
<i>Vaginal Operations</i>		41
Parametrial fixation and anterior and posterior repair	24	
Urethroplasty	8	
(a) Kelly type	2	
(b) Tantalum plate	5	
(c) Fascia lata	1	
Anterior and posterior colporrhaphy	7	
Lefort colpocleisis	1	
Resection of vulva for tumor	1	

### Case Reports

The following cases are representative of our results in the patients studied in the various phases of this investigation.

CASE I.—S. K. (576418), a 58-year-old white woman, was admitted for hysterectomy and first degree uterine prolapse. On Feb. 19, 1948, parametrial fixation and anterior and posterior colporrhaphy were performed. For two days after operation patient was unable to

CASE 4.—T. M. (576774), a 40-year-old white housewife, was admitted for a fibroid uterus; on Feb. 17, 1948, a total hysterectomy and bilateral salpingo-oophorectomy were performed. For the first thirty hours postoperatively the patient did not void (Fig. 6). Catheterizations revealed 200 to 700 c.c. At thirty-four hours postoperatively, Furmethide was begun orally, resulting in the initiating of spontaneous voiding of from 100 to 160 c.c. Catheterized urine volume dropped precipitously so that after two days residual was only 25 c.c. Spontaneous voiding of large amounts continued and patient was discharged.

The authors are indebted to Dr. Arthur M. Davids for permission to use his records of this case.

CASE 5.—F. D. (576796), a 42-year-old white parous woman, was admitted, complaining of urinary stress incontinence. On Feb. 19, 1948, a fascia lata urethroplasty, and anterior and posterior colporrhaphy were performed. For eighteen hours after operation no voiding occurred (Fig. 7). Catheterizations revealed urine volumes of from 100 to 300 c.c. Furmethide was started, resulting in prompt urination of 300 to 400 c.c. with residuals of 25 c.c. Furmethide therapy was discontinued after two days and spontaneous voidings occurred thereafter.

CASE 6.—C. L. (580045), a woman, aged 65, underwent operation on May 8, 1948, for complete uterine prolapse with eversion of the vagina. Parametrial fixation, and anterior and posterior colporrhaphy were performed. Two vaginal packings were left in place. Five hours after the operation patient received 10 mg. Furmethide and four hours later she voided 200 c.c. Two hours later she received a second dose of Furmethide and one-half hour later she again voided. Furmethide was continued for one more day and spontaneous micturition continued. Such an extensive operation usually requires from two to five days of catheterization. In this case, PTAI resulted in early voiding without any catheterization.

CASE 7.—B. S. (577690) (Failure No. 1). A 52-year-old white, Jewish, para ii, gravida ii, diabetic widow was admitted because of a large cystocele and prolapse of the cervical stump. A supravaginal hysterectomy and bilateral salpingo-oophorectomy were performed in 1934 for fibroids and adenomyosis. Urine on admission showed a two plus albumin with many white blood cells in clumps. Diabetic status was satisfactorily controlled and on March 18, 1948, a parametrial fixation, and anterior and posterior colporrhaphy were performed. Furmethide orally, 10 mg. three times a day, was begun postoperatively; only two doses were administered. The drug was stopped by a member of the house staff because of profuse salivation. Urine cultures revealed *Staphylococcus aureus*, *Bacillus coli*, enterococcus and *Bacillus pyocyaneus*; this urinary tract infection was treated with sulfadiazine and later with streptomycin. Because of bladder sediment and inability to void, an indwelling catheter with tidal drainage was continued from the second to the fifteenth postoperative days. After removal of the catheter, spontaneous voiding began. On the twentieth day, urine was clear and micturition was normal; patient was discharged on the twenty-second day with a good postoperative result.

CASE 8.—T. C. (578240) (Failure No. 2). A 53-year-old white, para iii, gravida iv was admitted on March 22, 1948, because of third degree uterine prolapse. The vaginal mucosa was found to be dry and paper thin; this condition was treated with stilbestrol, 5 mg. daily for six days. On April 1, 1948, a parametrial fixation, and anterior and posterior colporrhaphy were performed. At the time of operation the vaginal mucosa was found to be markedly thickened and edematous. Postoperatively, an indwelling catheter was introduced for four days and prophylactic sulfadiazine was administered. Urine culture showed enterococcus. On the fifth postoperative day, Furmethide was begun orally but voiding failed to take place and the drug was discontinued after forty-eight hours; repeated catheterizations were required. The external urethral meatus was markedly swollen and edematous; a large area of the suture line along the anterior vaginal wall showed necrosis. Hot baths and heat lamp applied to the perineum were begun. Finally the edema began to subside and Furmethide was again begun on the fifteenth postoperative day. Voiding started on the following day. Further course was uneventful and she was discharged on the eighteenth postoperative day.

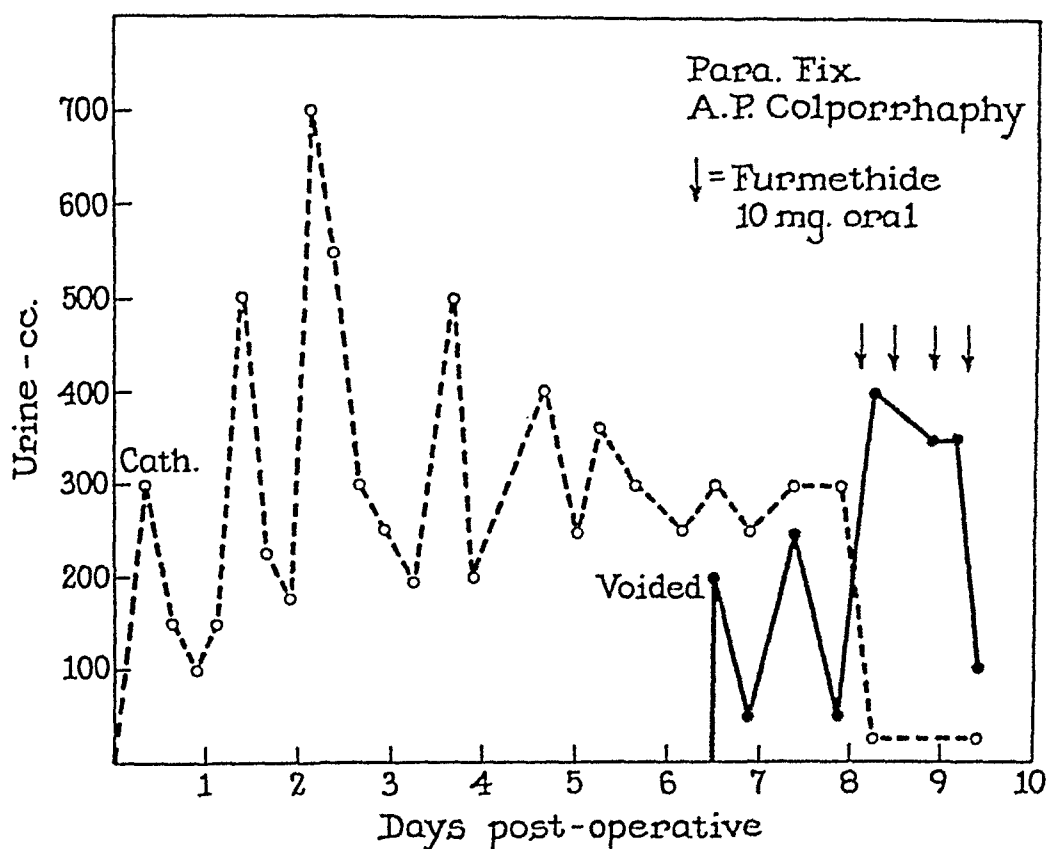


Fig. 4.

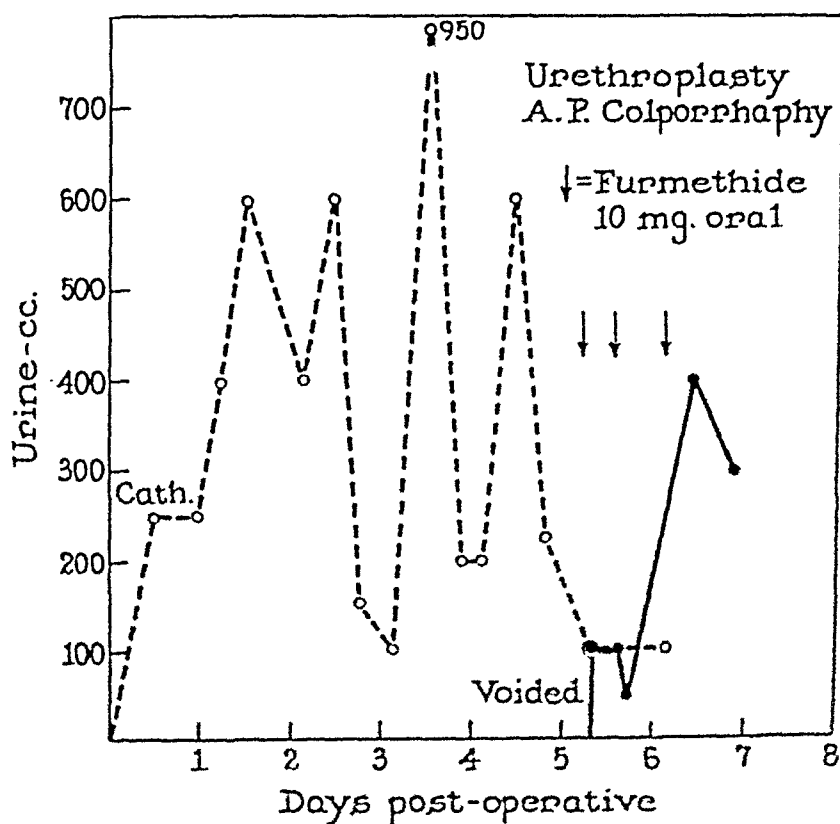


Fig. 5.

### Comment

Cases 1 and 2 are representative of the overflow type of micturition with large residuals and with protracted periods of postoperative distention. Following the use of Furmethide, prompt relief of the distention and return to normal micturition resulted. Cases 3, 4, and 5 are examples in which no voiding occurred prior to Furmethide; treatment with FTAI resulted in prompt voiding with continued spontaneous emptying. In this second group, the use of the drug was begun at various postoperative times before any routine method of administration was established. Case 6 represents the present method of administration four to five hours following the operation without the use of routine catheterization. In this case, immediate spontaneous voiding occurred and no catheterization was required.

In Cases 7 and 8 Furmethide failed to initiate normal micturition; the authors believe that several factors were in operation. Both cases had severe urinary infection and superimposed mechanical trauma produced by the use of indwelling catheters. In the first case, initial trial was limited to two doses only; the drug was discontinued because of minor side effects and misinterpretation of the importance of salivation and perspiration. In the second case, edema and later necrosis of the anterior vaginal wall and external urethral meatus prevented normal painless micturition. Severe tenesmus was also present. Catheterization was continued until the local infection had subsided.

In gynecological surgery, urinary retention remains an important problem during the immediate postoperative period. Especially is this true in operative cases that involve the anterior vaginal wall and urethrovesical neck. In this group of one hundred patients, the use of a new parasympathomimetic drug has been of value in initiating normal micturition with good emptying of the bladder, and greatly reducing the number of catheterizations. In cases of protracted postoperative urinary retention, this drug was of definite value in initiating spontaneous micturition and removing the need for further catheterization. More recently, this drug has been administered prophylactically in the immediate postoperative period requiring no catheterization. In obstruction of the urethra or vesical neck, or in severe urinary infection, the drug is contraindicated. The authors believe that this initial investigation has indicated that FTAI has a definite place in the armamentarium of the gynecological surgeon in the prophylaxis and treatment of urinary dysfunction following pelvic surgery.

### Summary and Conclusions

1. Furmethide was administered for postoperative urinary retention following gynecological surgery in one hundred cases.
2. No serious toxic effects were observed.
3. The routine use of FTAI orally in doses of 10 mg. three times a day is an adjuvant in the prevention of urinary retention following gynecological surgery.

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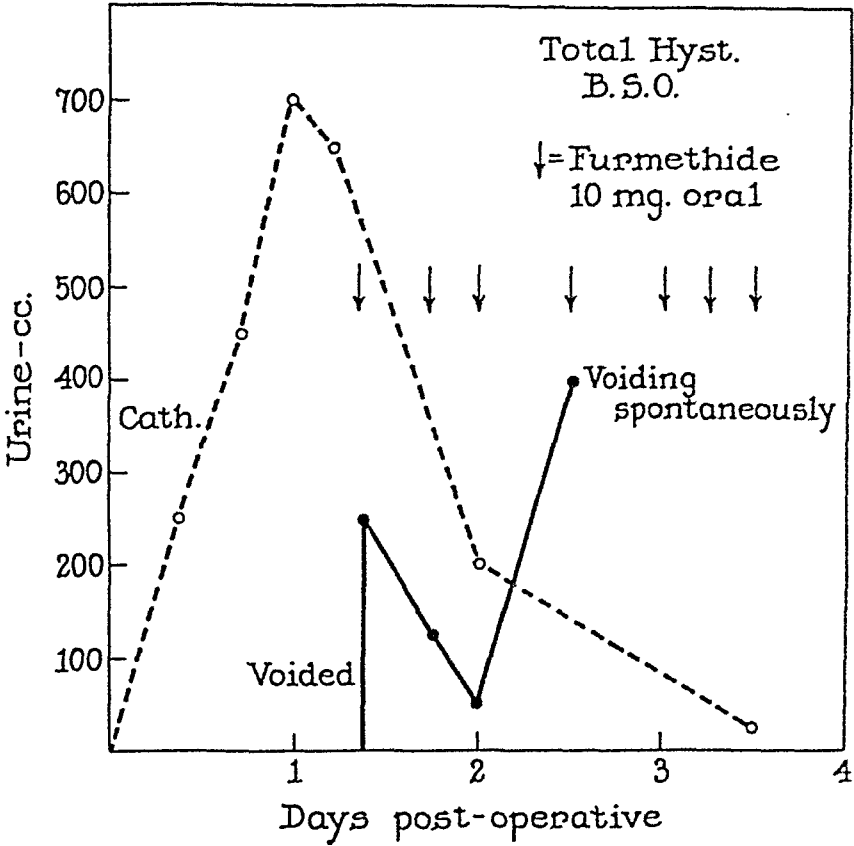


Fig. 6.

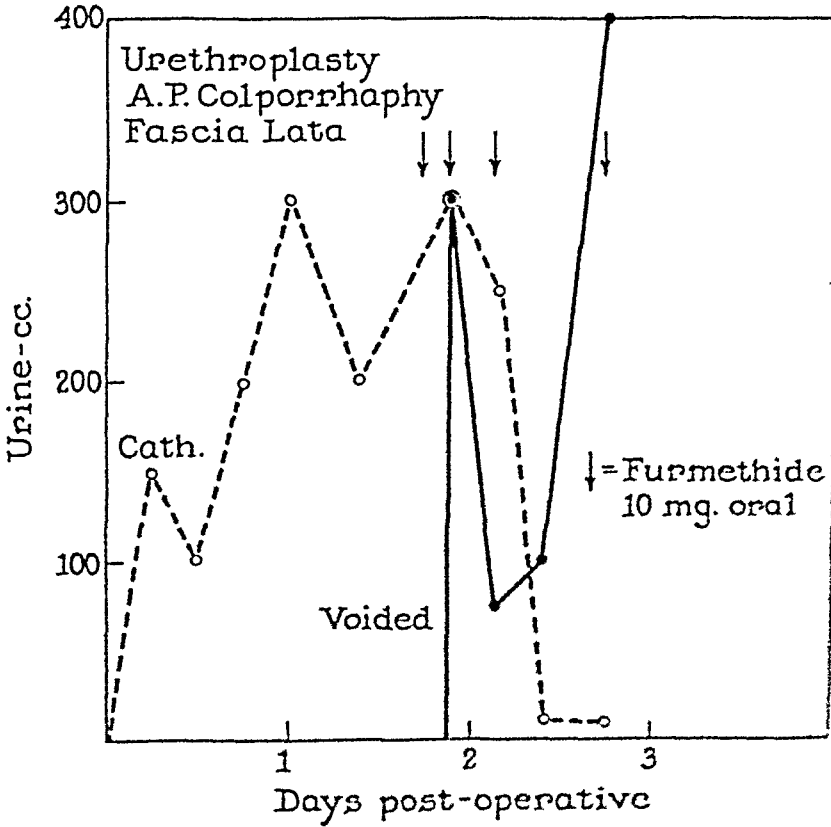


Fig. 7.



Cerebral tissues show hyperchromatic granules, vacuolization, and fragmentation of the tissues. This is most marked in the anterior hypothalamus.

Adair, Hunt, and Arnell<sup>2</sup> analyzed vascular collapse in toxemias of pregnancy and found a marked fall of blood pressure, prior to delivery and unaccompanied by hemorrhage. McIlroy<sup>3</sup> concluded that shock associated with the puerperal state was due to toxemia. DeLee<sup>4</sup> confirmed this and stated that syncope during eclampsia is attended by acute pulmonary edema and that the condition resembles anaphylaxis. Necropsy findings supported this. In this connection DeLee has stated, "We believe that the nephritis (in eclampsia) is only part of the general picture affecting all the capillaries and body tissues." And Moon<sup>5</sup> writes, "Most of the pathologic studies on eclampsia have emphasized the renal abnormalities and have failed to record the appearance seen elsewhere. When the conditions in other viscera have been described they conform closely to the pathology of shock."

Thus, pathologic findings in eclampsia are suggestive of a histamine or histamine-like reaction.

Chesley<sup>6</sup> found that pregnant women who have more "available water" than normal develop toxemia seven times as often as normal subjects. When excessive "available water" and lowered serum protein were found together, there was an increased disposition to eclampsia. However, he states<sup>6</sup> that oncotic pressure of tissue fluid is not increased in toxemia and capillary permeability cannot be great as indicated by the low protein content of edema fluid. Also, rate of filtration from arm capillaries was less than normal due to increased hydrostatic pressure of the tissue spaces.

McLennan<sup>7</sup> showed that the filtration through capillaries in pregnant toxemic women is less than filtration rate in normal pregnancy, because of the presence of edema.

Studies on blood volumes in pregnant women have been in agreement that there is a gain in total volume of blood and that there is hydremia, but they do not agree on amount. Recently, Macarthur<sup>8</sup> showed that there was a relative hemoconcentration in toxemic women.

In spite of some conflicting evidence, I felt that there are enough pathologic findings to support the thesis that the manifestations of pre-eclamptic toxemia are due to some histamine or histamine-like substance. The work of Smith and Smith<sup>9</sup> on the presence of "menstrual toxin" gave added support, in that it might be the injuring agent which would release histamine by its noxious action.

Thus, I felt that a trial with an antihistamine drug on a pre-eclamptic woman would be justified, although a careful search of the literature failed to reveal any previous use of antihistamine drugs for this purpose.

### Material

Patients were chosen from the prenatal clinic of the Newark City Hospital. Ninety per cent of these patients are Negro and are in the low-income group. They frequently miss their clinic appointments even though they might be ill and are informed of the importance of prenatal visits. Some who are acutely ill and are urged to enter the hospital will refuse to do so and have to be treated as ambulatory cases. The visiting nurses of this clinic see patients who miss appointments at home, take their blood pressures, and try to see that orders are

## THE EFFECT OF TREATMENT WITH AN ANTIHISTAMINIC DRUG ON BLOOD PRESSURE AND URINE IN PREGNANT WOMEN

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NO ADEQUATE explanation has yet been advanced for the pathogenesis of pre-eclamptic toxemia. It seems to me that there is an impressive parallel, however, between these disorders and the type of shock produced by histamine-like substances. Recent studies<sup>1</sup> show that in shock there is, at first, a rise in blood pressure. This remains high until decompensation takes place. In this connection, Moon<sup>1</sup> writes:

“Any kind of injury causes the adjacent capillaries to dilate and become more permeable. This is a local physiologic effect resulting in inflammatory hyperemia. The action of osmosis and maintenance of fluid balance between the blood and the tissues are absolutely conditioned upon the presence of a normal semi-permeable membrane between those compartments.”

Moon continues by explaining that conditions which affect the endothelium adversely always alter this quality of semi-permeability: “Abnormal endothelial permeability upsets the mechanism of fluid balance and of absorption by which the blood is maintained at a composition and volume within physiologic limits; as a result, the blood volume decreases, and its concentration increases. Disturbance of renal function results, for the process of filtration through the glomerular endothelium is lowered progressively with hemoconcentration.”

Shock occurs in varying degrees, and develops with varying rapidity. We are here concerned with that type that does not develop too rapidly.

Beside the findings as above stated, there is, in a slow-developing case of shock, “A decrease in the alkaline reserve, a hemoconcentration, a decrease in the plasma ratio of albumin to globulin, decline of the sodium, and an increase of the potassium in the blood.” In shock there is also a retention of nitrogenous waste. The urine is concentrated, its specific gravity elevated, and it contains casts, albumin, and red cells.

Postmortem examination of animals or human beings who die in shock reveals congestion of the pleural and peritoneal surfaces. The venules of the omentum are congested, the mucosa of the intestinal tract develops a deep cyanotic color. The lungs, liver, and kidneys become deeply congested. The tissues of the viscera exhibit distention of the capillaries and the venules. The parenchymatous or granular degeneration of the kidney is sometimes slight and sometimes marked. It is evidenced by the usual slight pallor and swelling of the organ, except when the pallor is overshadowed by congestion, and by fine granulation and vacuolization of the cytoplasm seen microscopically. Necrosis in the liver may concentrate around the central vein or may be irregularly distributed. These areas of parenchymatous degeneration are probably due to anoxia which is a marked feature of latter stages of shock.

Pyribenzamine was administered. Patient 1 had an initial drop in blood pressure from 142/88 to 130/80, but then it gradually rose to 144/80 and a still-birth resulted. Patient 3 had to be admitted to the hospital for a pre-eclampsia and delivered a living child six days after admission. She had a hypertension in her last pregnancy which had resulted in a stillborn. Patients 3, 6, 8, and 9 had histories of hypertension in one or more previous pregnancies.

Patient 8 stopped Pyribenzamine two weeks before delivery and there was a gradual rise in her blood pressure from 124/60 to 138/80 and it remained at this level until delivery.

TABLE II. GROUP II. HYPERTENSION

PATIENT NO.	GRAVIDITY	AGE	WEEK OF GESTATION TREATMENT* STARTED	TOTAL NUMBER OF WEEKS TREATED	RESULTS
1	i	18	36	4	Blood pressure 142/88 to 130/80 in one week. Gradually climbed to 144/80. Still-birth.
2	ii	20	32	8	Blood pressure 152/80 to 120/60 in two weeks. Remained at this level.
3	vi	29	32	8	Blood pressure 140/80, climbed steadily to 160/110. Admitted for pre-eclampsia.
4	i	20	28	8	Blood pressure 140/82 to 100/50 in two weeks. Remained at this level.
5	iii	23	24	12	Blood pressure 146/84 to 120/70 in three weeks. Remained at this level.
6	vi	40	34	6	Blood pressure 141/90 to 114/58 in two weeks. Remained at this level.
7	vi	29	36	4	Blood pressure 148/84 to 134/78 in one week. Remained at this level.
8	ii	22	36	2	Blood pressure 150/90 to 124/66 in one week. Patient stopped medication and blood pressure rose to 138/80 in two weeks.
9	iii	28	36	4	Blood pressure 154/90 to 118/70 in one week. Next week was 130/80. Continued at this level until delivery.
10	iii	21	35	5	Blood pressure 140/80 to 116/66 in one week. Remained at this level.
11	i	17	37	3	Blood pressure 150/90 to 130/70 in one week. Following week 134/80. Remained until delivery.
12	ii	23	36	4	Blood pressure 140/80 to 106/50 in one week. Remained at this level.

\*Treatment 50 mg. Pyribenzamine three times daily.

*Group III. Albuminuria and Hypertension.*—In this category fifteen patients were studied. Twelve patients showed a substantial drop in the blood pressure under medication. In the other three (Patients 12, 13, and 15) there was either no change in the blood pressure or there was a definite rise, and no effect was seen in the albuminuria. In Patient 11 there was a drop in the blood pressure but no effect was noted on the albuminuria.

Several of the patients' histories during this study require closer attention:

**PATIENT 2.**—Under medication, her blood pressure dropped satisfactorily. When Pyribenzamine was discontinued, her blood pressure rose sharply and she had to be admitted to the hospital with a diagnosis of pre-eclampsia. This happened twice during her pregnancy. After her second admission she continued Pyribenzamine and no further trouble ensued.

carried out as to rest, salt and fluid restriction, etc. If a rise in blood pressure is noted, albumin is found in the urine, or an excessive gain in weight is noted, the patients are placed on a sodium-poor diet and fluids are restricted. If, in spite of this regime, blood pressures still remain high, or albuminuria still persists, they receive 50 mg. of Pyribenzamine three times a day in conjunction with the salt and fluid restriction. This regime was tried only on patients in the clinic and was not followed in the hospital. Blood pressures were considered elevated if they were above 140/80 in patients whose normals were below this as noted in former visits to the clinic.

### Patients Treated

The patients were divided into three groups:

Group I. No rise in blood pressure but albumin persisting in the urine.

Group II. Rise in blood pressure but no albumin in the urine.

Group III. Both rise in blood pressure and albumin in the urine.

*Group I. Albuminuria Only.*—All urines were noneatheterized. Albumin was determined by heat and acetic acid and was reported as one, two, three, or four plus according to the density of the cloud.

Thirteen patients in this group were treated with 50 mg. of Pyribenzamine three times daily together with salt restriction. Only patients who did not respond to the usual therapy of salt restriction were so treated.

TABLE I. GROUP I. ALBUMINURIA

PATIENT NO.	GRAVID- ITY	AGE	WEEK OF GESTA- TION TREAT- MENT*	NO. OF WEEKS MEDICA- TION TAKEN	AMOUNT OF ALBU- MINU- RIA BEFORE TREAT- MENT		RESULTS
1	i	15	34	6	2+	No change	
2	iii	23	37	3	3+	Urine negative in two weeks	
3	i	16	30	7	2+	Urine 1+ in one week. Remained until delivery	
4	i	17	37	3	1+	Urine negative in one week	
5	i	17	32	2	1+	Urine negative in one week. Al- bumin reappeared one week after medication discontinued	
6	i	23	36	4	1+	Urine negative in one week	
7	i	20	34	2	1+	Urine negative in one week	
8	i	22	36	4	2+	Urine negative in three weeks	
9	iii	39	30	9	1+	Urine negative in one week	
10	ii	31	30	2	2+	Urine negative in one week	
11	ii	18	34	2	1+	Urine negative in one week	
12	i	18	32	4	1+	Urine negative in one week	
13	i	21	37	3	1+	Urine negative in one week	

\*Fifty milligrams Pyribenzamine three times daily.

The urine did not become free of albumin in two patients (Patients 1 and 3) of this group. Both of them were primiparas and both were in the very young age group. In only one patient (Patient 5) did albumin again reappear in the urine after the discontinuance of Pyribenzamine. In ten patients, the urine was free of albumin after one week of this therapy.

*Group II. Hypertension Only.*—Twelve patients were treated in this group. Ten patients had a substantial fall in blood pressure which was maintained until delivery. On two patients (Patients 1 and 3) no improvement was noted after

benzamine were then ordered three times daily. Her blood pressure gradually dropped to 126/76 in about three weeks and her urine contained a one plus albumin. The next three weeks she did not appear in clinic and no medication was given. Her blood pressure gradually climbed to 170/90 and her urine contained a three plus albumin. She was hospitalized at this time and she delivered a living child a week later.

PATIENT 9.—This patient had a history of pre-eclampsia in her second and third pregnancies. Under Pyribenzamine therapy, her blood pressure dropped from 144/80 to 126/52 in one week. This medication was discontinued and in three weeks time her blood pressure rose to 150/100. Under Pyribenzamine her blood pressure again gradually dropped to 130/80 and remained at this level until delivery.

PATIENT 11.—This patient's blood pressure dropped under Pyribenzamine from 140/80 to 116/80 in two weeks. No change occurred in the albuminuria (two plus when medication was started). Her blood pressure gradually climbed and reached 132/66 in three weeks. It remained at this last level until delivery.

PATIENT 12.—On a salt-free diet, this patient's blood pressure dropped from 140/90 to 112/70. However, her urine still contained a three plus albumin. Pyribenzamine, 50 mg. three times daily, was prescribed. Four days after Pyribenzamine was ordered, her blood pressure was 170/110. She was admitted to the hospital for a pre-eclamptic toxemia for a period of one week. When she returned to the clinic a day after discharge from the hospital her blood pressure was 132/76 and she had a three plus albuminuria. Again 50 mg. three times daily were ordered and her blood pressure rose to 136/100. Her urine still contained a three plus albuminuria. She delivered soon after this visit to the clinic, three weeks prematurely, and her baby died two days after birth.

PATIENT 13.—This patient's blood pressure rose suddenly from 120/80 to 170/90 with a three plus albuminuria. One hundred mg. Pyribenzamine three times daily were ordered. No change occurred in the hypertension or the albuminuria in two days and the patient was admitted to the hospital for pre-eclamptic toxemia. She returned to the clinic two weeks later at which time her blood pressure was 132/82 and her urine contained three plus albumin. She was placed on 50 mg. Pyribenzamine three times daily. No change occurred in the hypertension or the amount of albumin in the urine. She delivered a stillborn infant eight weeks later.

PATIENT 15.—This patient was started on 50 mg. Pyribenzamine when her blood pressure was 132/72 and her urine contained a one plus albumin. Her blood pressure gradually climbed to 152/74 and no change occurred in the amount of albumin in the urine.

### Summary

1. Forty patients were treated with Pyribenzamine.
2. Thirteen patients had albuminuria:
  - a. Eleven became albumin free.
  - b. Two showed no improvement.
3. Twelve patients were treated for hypertension:
  - a. Ten showed a definite drop in blood pressure.
  - b. Two were not benefited.
4. Fifteen patients with hypertension and albuminuria were treated:
  - a. Twelve showed a definite drop in blood pressure. In eleven of these, the urine became albumin free and they improved.

TABLE III. GROUP III. HYPERTENSION AND ALBUMINURIA

PATIENT NO.	AGE	GRAVIDITY	WEEK STARTED MEDICATION*	RESULTS			
				BLOOD PRESSURE	URINE		DELIVERY
1	29	ii	30	150/90 to 120/80 in one week	2+ albumin to negative in one week		Living
2	29	i	24	166/70 to 120/68 in three weeks	1+ albumin to negative in one week		Living
3	21	i	24	150/90 to 122/70 in one week	2+ albumin to negative in one week		Living
4	24	iii	37	140/80 to 124/80 in two weeks	1+ albumin to negative in one week		Living
5	17	i	35	144/82 to 124/80 in one week	1+ albumin to negative in one week		Living
6	37	iii	36	146/80 to 110/76 in two weeks	1+ albumin to negative in one week		Living
7	34	viii	32	154/90 to 132/80 in two weeks	1+ albumin to negative in one week		Living
8	32	xi	32†	184/90 to 126/76 in three weeks	3+ albumin to 1+ in three weeks		Living
9	26	vi	32	150/100 to 130/80 in one week	1+ albumin to negative in one week		Living
10	21	iii	34	140/80 to 112/80 in two weeks	1+ albumin to negative in one week		Living
11	37	v	32	140/80 to 116/80 in two weeks	2+ albumin. No change		Living
12	23	i	34	132/76 to 136/100 in one week	3+ albumin. No change		†
13	27	i	30	132/82. No change	3+ albumin. No change		Still-birth
14	16	i	38	154/78 to 148/88 in one week	2+ albumin. No change		Living
15	42	v	32	132/72 to 152/74 in two weeks	1+ albumin. No change		Living

\*Fifty milligrams Pyribenzamine three times daily.

†For first two days medication 100 mg. Pyribenzamine three times daily.

‡Birth three weeks premature, died two days after delivery.

PATIENT 3.—A similar situation existed in this patient. Her blood pressure when medication was started was 144/90 with a two plus albuminuria. In one week, her urine was negative and her blood pressure was 134/80. She then disappeared from the clinic for eight weeks. On her return, her blood pressure was 150/90, urine was negative. Under Pyribenzamine in one week her blood pressure was 122/70 and remained at this level until delivery.

PATIENT 7.—This patient had three stillbirths. She had pre-eclamptic toxemia during her last five pregnancies. She was at first treated when her blood pressure was 140/90 with a one plus albuminuria. In one week, her urine was negative and her blood pressure was 120/80. Medication was discontinued at this time by error and the following week her blood pressure was 154/90. Her urine at this time was negative. Under Pyribenzamine, her blood pressure reached 132/80 and remained at this level until one week before delivery, when Pyribenzamine was again discontinued by the patient. Just before going into labor her blood pressure was 150/110.

PATIENT 8.—This patient has had severe pre-eclampsia since her fifth pregnancy. Her last pregnancy ended in a stillbirth. She placed herself on a salt-poor diet two months before her appearance at the clinic and had been taking, daily, epsom salts for three weeks. At her first visit, her blood pressure was 184/90 with a three plus albuminuria. She refused to be hospitalized and was placed on 100 mg. Pyribenzamine three times daily. In two days her blood pressure was 162/90 and her urine contained a two plus albumin. Fifty mg. of Pyri-

# NEW METHOD OF DOVETAIL APPROXIMATION OF THE LIGAMENTS IN VAGINAL HYSTERECTOMY FOR PROCIDENTIA\*

## A Preliminary Report

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THE purpose of this paper is to present a variation in the handling of the stumps of the broad ligaments during vaginal hysterectomy for procidentia. This modification adds to the support of the bladder and vaginal vault, thus diminishing the likelihood of descent of the bladder with recurrence of urinary symptoms and preventing subsequent prolapse of the vaginal vault.

The indications for vaginal hysterectomy and its merits will not be discussed here, as these have been adequately treated elsewhere in the medical literature.<sup>1,2,14</sup>

Unfortunately, it is difficult to assess the value of the various procedures which have, from time to time, been suggested for the management of the stumps of the broad ligaments and repair of the pelvic floor in vaginal hysterectomy for prolapse. For a time, during the years following the report of the Mayo-Ward technique with imbrication of the broad ligaments, it seemed as if this method was indeed the best answer to the problem, and that a standard method had at last been attained. Recently, however, a number of innovations in technique have been suggested, and several articles have appeared, taking up anew the subject of the anatomy and physiology of the structures involved.<sup>3,5,8,12</sup> These facts would seem to indicate that some uncertainty has arisen as to the efficacy of the Mayo-Ward technique. Follow-up reports and statistics of end results are so few and far between, that we cannot look to them for help in selecting this or that method as likely to yield best results.

There have been several articles written attributing to various anatomical structures the major importance in uterine support. Among these are articles by Mengert,<sup>3</sup> Barnes,<sup>4</sup> W. Shaw,<sup>5</sup> Harrison,<sup>7</sup> and Power.<sup>8</sup>

Just as different surgeons consider various anatomical structures as the major source of uterine support, so various operators have devised techniques in their efforts to get excellent results with vaginal hysterectomy for procidentia, as the Mayo-Ward technique, the Gellhorn-Emmert<sup>1,2</sup> modification of the Dickinson technique, the Veenboer and Kooistra<sup>6</sup> technique, the Heaney<sup>9</sup> technique, the Campbell<sup>10</sup> technique, and many others.

The results reported from series of cases operated upon by these different techniques show an incidence of faulty results varying from 4 to 30 per cent of the cases. Most of the poor results were recurrences of cystocele, rectocele, enterocele, and urethrocele, and shortening of the vagina. The common feature of

\*Presented at a meeting of the Obstetrical Society of Philadelphia, Pa., May 6, 1948.

b. Three were not benefited either in hypertension or albuminuria. One of these had a stillborn infant and one had a premature infant that died two days after birth.

### Conclusion

From this study, I believe that there is some value in the use of an antihistaminic drug in pregnant women with a rise in blood pressure, albuminuria, or a combination of both. Further confirmatory evidence would be desirable.

I would like to express my appreciation to Drs. John N. Pannullo, William Antopol, and Louis E. Goldberg for their criticism and help.

Pyribenzamine was supplied by Ciba Pharmaceutical Products, Inc.

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Fig. 3.

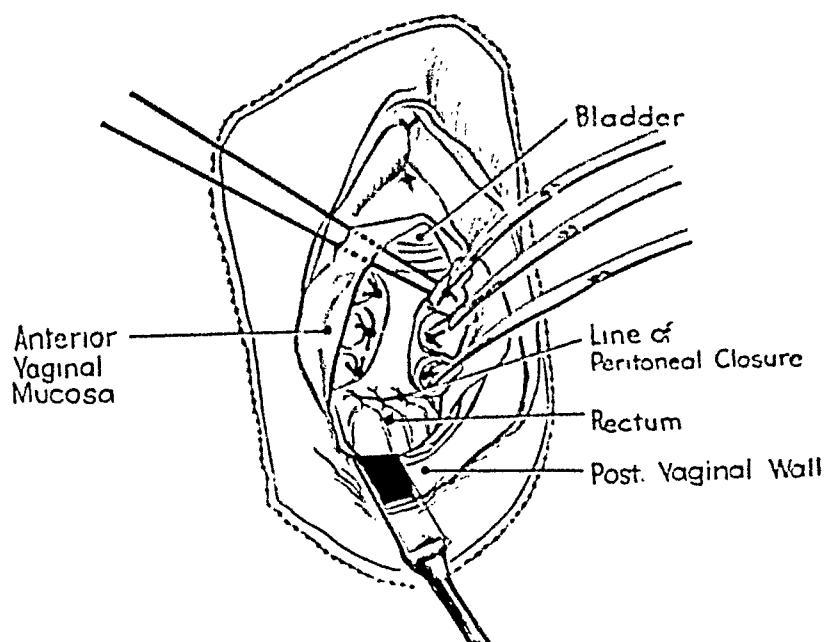
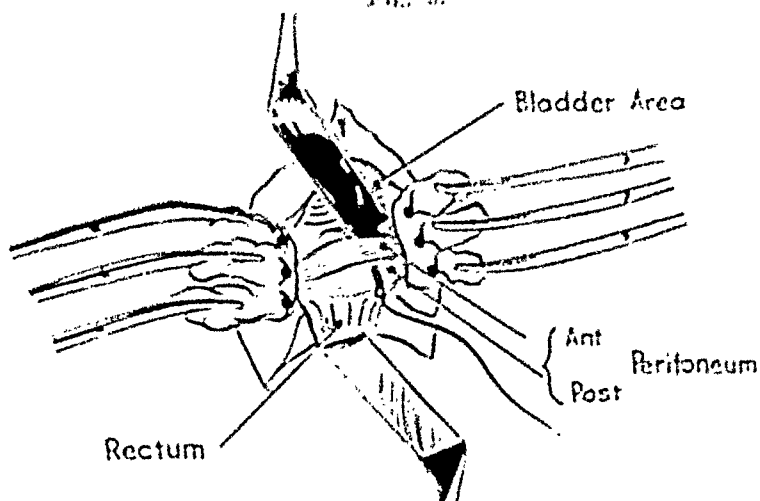


Fig. 4.

all these operative interventions suggested heretofore has been the approximation of the ligaments in the midline, and it is exactly from this particular procedure that the present author has deviated.

With the dovetail approximation of the ligaments here proposed, the support of the bladder and vaginal vault is strengthened, thus diminishing the possibility of descent of the bladder with recurrence of urinary symptoms and preventing prolapse of the vaginal vault.

In all, twenty-five patients have been operated upon by this technique, and have been followed up from one to four years postoperatively. These patients are all free from recurrence of urinary symptoms and prolapse of the vaginal vault.

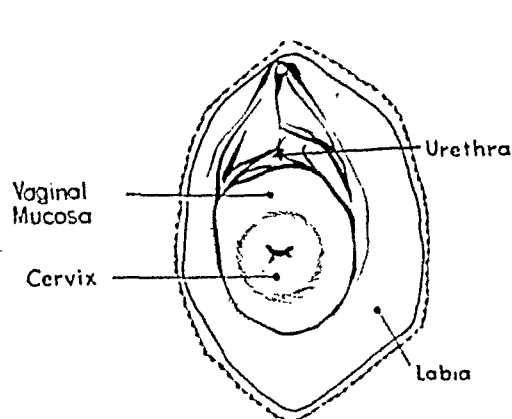


Fig. 1.

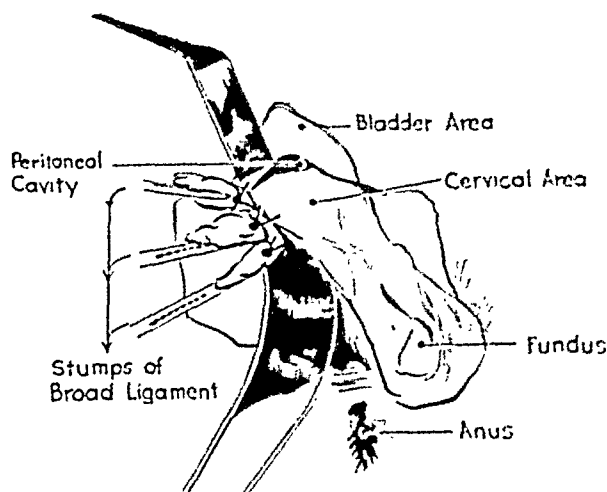


Fig. 2.

## Procedure

After the patient has been anesthetized (most frequently fractional spinal anesthesia), the patient is catheterized. The practicability of a vaginal hysterectomy is reassessed during bimanual examination (Fig. 1). The cervix is exposed, grasped, and pulled down to its limit. A racquet-shaped incision, through the vaginal mucosa with its point just posterior to the urethral meatus, is made around the cervix. The bladder is freed from the uterus by blunt dissection and pushed up. An incision is made through the peritoneum in the posterior vaginal vault, and two fingers are inserted to be used as a guide in making an anterior entry into the peritoneal cavity. The fundus of the uterus is delivered between the bladder and the cervix. Each broad ligament is then clamped and ligated in three sections from above downward (Fig. 2) and the clamps left in place. The uterus is then removed.

The repair is begun by closing the peritoneum above the stumps of the broad ligaments with a continuous suture (Fig. 3). Mattress sutures are then placed in each segment of the broad ligaments (Fig. 4) distal to the ligatures, and the ends left long. The pelvic peritoneum and cellular tissue are then freed by blunt dissection from the vaginal mucosa. The long ends of the sutures of the right upper segment are passed through the vaginal mucosa on the left (Fig. 5), about  $1\frac{1}{2}$  inches from the urethral meatus, and tied. The sutures of the left upper segment are passed through the right vaginal mucosa in the same way. The remaining stumps are anchored alternatively in the same way, being attached further posteriorly to the vaginal mucosa. The vaginal mucosa is trimmed and closed with a continuous suture (Fig. 6). A catheter is placed into the urethra and bladder. A posterior colporrhaphy and perineorrhaphy are then performed.

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248 EAST 21ST STREET.

### Discussion

DR. ROBERT A. KIMBROUGH, JR.—I would like to ask the essayist if he pays any especial attention to fixing the top of the vagina to the uterosacral ligaments as a measure for obtaining vaginal depth. I was interested in the statement "no appreciable shortening of the vagina occurs following this operation." I would like a definition for the word "appreciable" in this statement. I am still looking for a method which will give no shortening of the vagina.

DR. GEORGE A. HAHN.—I have had the privilege of seeing Dr. Stuckert do a number of these vaginal hysterectomies and to me this seems to be a very logical method. The point that sticks in my mind was that a sort of hammock or basket was formed by the tissues pulled criss-cross so that the more pressure was exerted downward, the greater the tension pulled upward. I also saw several patients postoperatively and they had excellent postoperative results. I was impressed by the number of enteroceles mentioned in this report as encountered by other methods and was interested to know if they had any result like this in their procedure.

DR. JAMES R. HERRON.—In answer to Dr. Farrell's question, we found no excessive tension causing lower abdominal discomfort postoperatively in a number of procedures nor has there been any difficulty in handling the cases. Dr. Hahn, we have had no enteroceles so far. Dr. Scheffey, we have had no postoperative bleeding. Dr. Kimbrough, there has been no special suturing of the vaginal vault to the uterosacral ligaments. As to what is appreciable shortening of the vagina, I suppose that has a lot to do with the patients and their activities. Dr. Montgomery, we have had no unusual bladder disturbances. We usually catheterize the patient for five to seven days.

DR. STUCKERT (Closing).—As far as the questions that have been asked, I might say again, we have had no postoperative hemorrhage of any kind and as far as the bladder is concerned, the postoperative procedure is to keep a catheter in the bladder for possibly six days or so, irrigating the bladder occasionally and then removing the catheter and subsequently catheterizing the patient every eight or ten hours if necessary. Eventually they void without any difficulty whatsoever.

I realize we are reporting only a small number of cases but previously it has been the author's unpleasant experience to have cystoceles and enteroceles re-form and prolapse of the vaginal wall occur. With this thought in mind, it was decided to treat the broad ligaments as stated tonight.

As Dr. Hahn has stated, by drawing the stumps of the broad ligaments across to the opposite side of the vaginal wall, one develops or produces a so-called pelvic diaphragm upon which the bladder will rest. We have followed up these patients either by letter or by seeing them personally and, so far, we have not had a single patient complain of any bladder disturbance.

There is no evidence of any prolapse of the vaginal wall or the recurrence of a cystocele. As far as the length of the vagina is concerned, we have had no complaints about that. Apparently, from examining these patients postoperatively from time to time, I would say that, while the vaginal canal may be shortened slightly, it is of no inconvenience to the patient.

The present report, with a record of no anatomical recurrences in a series of twenty-five cases, indicates that the procedure here described will prove to be of real value in improving the end results of vaginal hysterectomy for procidentia.

Fig. 5.

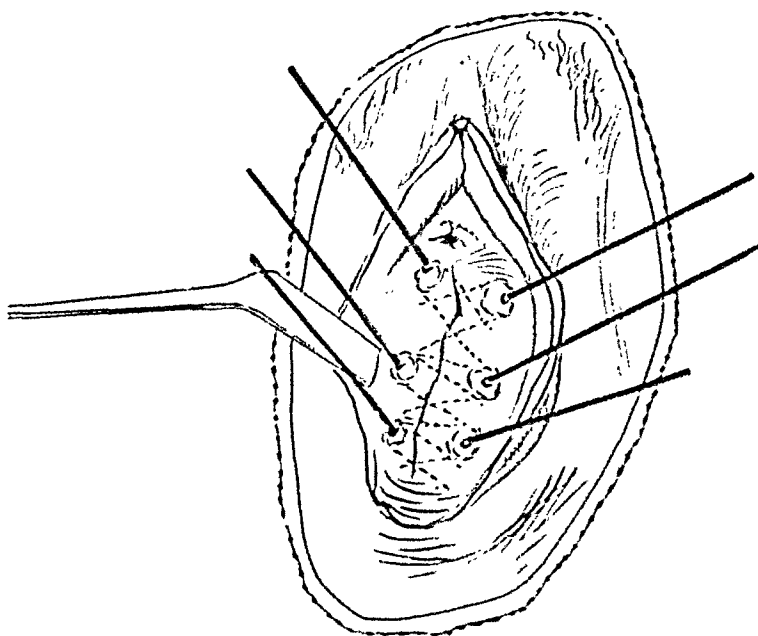
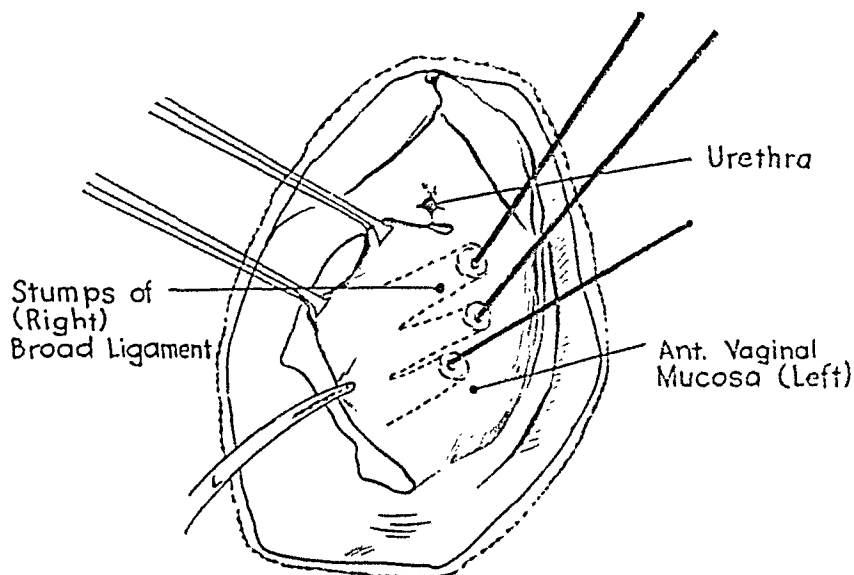


Fig. 6.

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The observation had previously been made by us that certain fatty acids and their salts (propionic and undecylenic acid) in a suitable ointment base have a marked antipruritic effect when used on the vulvar and perianal skin. All of our cases were treated in the same manner. A 15 per cent sodium propionate ointment was rubbed into the vulvar and perianal skin two or three times daily. A vanishing cream base containing a wetting agent, 1 per cent aerosol, was found to be most suitable. Patients with vaginal discharge were instructed to use a 5 per cent sodium propionate douche morning and night. In a number of cases, vaginal suppositories of 10 per cent sodium propionate in cocoa butter were used in conjunction with the application of the vulvar ointment. Petrolatum and carbowax bases were found to be too greasy for use in moist areas subject to friction. In the vast majority of cases the relief of symptoms was rapid and most gratifying.

### Results

A group of fifteen cases of diabetes with associated pruritus vulvae were treated. These patients were under treatment in the diabetic clinic and their diabetes was under control. The duration of symptoms varied from one month to three years. The vulva in these cases exhibited a fairly characteristic picture. The color varied from a salmon pink to a beefy red. The normal skin was replaced by a nonmarginated, moist, excoriated surface. The severe cases had marked abrasions of the skin which in the more widespread involved the intercrural regions. In eight, or over 50 per cent, of these patients relief was complete after treatment for one week. The remaining seven cases required two to four weeks for complete restoration to normal.

Eight cases of nondiabetic mycotic vulvovaginitis were treated. All of these cases had marked vaginitis with irritating discharge and severe pruritus vulvae. These patients were treated with a combination of 10 per cent sodium propionate vaginal suppositories twice daily and the application of 15 per cent sodium propionate ointment to the vulva two to three times daily. All but one of these patients responded uniformly well with disappearance of symptoms in one to three weeks. The vaginal mucosa and vulvar skin appeared normal at the termination of the treatment and no yeast fungi could be isolated. In one case, despite the relief of symptoms while under therapy, the vaginal discharge and itching returned within a week after cessation of treatment. This occurred after three successive courses of therapy.

Twenty-two cases of menopausal or atrophic vulvitis were treated in this series. The patients' ages ranged from 50 to 77 years and the duration of symptoms extended from one month to twelve years. The local pathology basically is an atrophy of the deep vulvar structures and is often associated with a thin, dry, waxy skin. This underlying picture can be complicated by all degrees of excoriation and infection resulting from scratching and poor hygiene. The worst case in this group was in a 77-year-old woman who had been suffering from pruritus for four years. The entire vulva and intercrural regions were excoriated and edematous. The response in this particular case was most impressive. At the end of three weeks this patient was symptom free with a vulvar skin which had completely epithelialized, was normally moist and did not have the shiny dry appearance characteristic of a woman of her age. In general, the menopausal cases required a longer treatment period for complete relief than did those patients suffering from mycotic vulvovaginitis. They were treated by local applications of 15 per cent to 20 per cent sodium propionate ointment two to three times daily. Most patients began to feel better after a few days and relief was progressive. Pruritus disappeared in a period varying from two to eight weeks. The local skin response was striking in this group of patients. At

## FATTY ACID THERAPY OF PRURITUS VULVAE

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**P**RURITUS vulvae is a distressing and common complaint which heretofore has not responded with ease to the usual therapeutic procedures. Analgesic ointments, x-ray and tattooing have all been used with varying and unpredictable results. The itching may be mild or of such severity that life is intolerable. The sleepless, haggard woman who has gone from doctor to doctor in futile search for relief is not an uncommon type of patient.

Pruritus vulvae is a diagnosis which expresses a symptom and not a cause. The success of any therapeutic endeavor in large measure rests upon an accurate diagnosis of the disease. The vulvar skin may appear normal or may show all degrees of excoriation, secondary infection, and lichenification. In many cases no cause can be found and this is the group usually considered to be psychogenic in origin.

The following table is a rough grouping to enable the physician to have a working diagnosis in treating these cases.

1. Pruritus vulvae as part of a generalized dermatosis (scabies, lichen planus, neurodermatitis, psoriasis, etc.).
2. Pruritus vulvae secondary to primary disease of the vulva (leucoplakia, kraurosis, contact dermatitis).
3. Pruritus vulvae secondary to menopausal changes (atrophic vulvitis).
4. Pruritus vulvae secondary to vulvovaginitis (trichomoniasis, mycotic vulvovaginitis, specific and nonspecific bacterial infections of the vagina and vulva, chemical vulvovaginitis, pruritus vulvae associated with diabetes, dermatophytosis).
5. Pruritus vulvae secondary to local infestations (pediculosis, enterobiasis, etc.).
6. Pruritus vulvae with no apparent cause. Psychogenic?

In this particular study all cases of pruritus vulvae in the out-patient department were referred to a special gynecological clinic where they were classified and treated by a team consisting of a gynecologist and dermatologist. A history was taken and the local lesion described in each case. A routine urine examination for sugar, and vaginal smears for *Trichomonas* and *Monilia* were done. Skin cultures and biopsies were performed when indicated. Each case was analyzed for its position in the etiological table given above. The cases accepted for study consisted of:

1. Diabetic vulvitis (clinical diabetes associated with acute eczematoid skin changes with and without demonstrable yeast organisms in the vaginal smears).
2. Mycotic vulvovaginitis (yeast-laden vaginal discharge with secondary vulvar eczematization).
3. Menopausal vulvitis (all cases of pruritus vulvae with onset at or after menopause and associated with atrophic skin changes on the vulva).
4. Unclassified as to cause but all associated with long-standing pruritus with secondary lichenification.

The physical atrophy of old age is paralleled by diminished secretory activity. It is logical to assume that the diminution of protective factors will permit the overgrowth of skin organisms with consequent local infection and sensitization to their products. The relief secured by the local application of sodium propionate indicates that this supposition is probably correct.

### Summary

The value of sodium propionate as an ointment, douche, and suppository has been shown in the treatment of pruritus vulvae due to a variety of causes. An unreported group of pruritus ani cases have also cleared under this therapy.

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the termination of treatment the skin no longer appeared dry, shiny, or scaly, but was moist and had a normal texture. Three patients in this group still complained of itching after two months of treatment. There had been marked improvement in the condition of the vulvar skin in each case but itching could not be completely relieved. The menopausal patient who has suffered from pruritus vulvae usually does not wish to stop the application of the ointment despite complete relief of symptoms. She fears return of itching. We have seen no ill effects from prolonged application of the ointment in these patients.

Two patients who had had vulvectomies for leucoplakia were treated because of persistent itching in the areas of the vulvectomy scars. Both patients were greatly relieved of the pruritus and in one of these cases there was a marked desquamation of the thickened epithelium at the skin margins of the vulvectomy scar. Following this desquamation a normal epithelium remained.

Four patients who had suffered from long-standing pruritus and had marked secondary lichenification were treated. In treating these patients, 1 per cent salicylic acid was added to 20 per cent sodium propionate ointment. The itching was completely relieved in three cases and partially in the fourth case. The therapy was prolonged in these cases and there was progressive desquamation of the thickened, pale, lichenified areas.

### Discussion

R. L. Alter et al.<sup>2</sup> treated a series of cases suffering from mycotic vulvovaginitis. They used a vaginal jelly containing sodium and calcium propionate and obtained excellent results. We have obtained similarly good results in this type of case using the fatty acids as a douche or vaginal suppository. The treatment is effective and the response rapid.

The contribution of this publication is the demonstration of the value of fatty acids in the treatment of pruritus vulvae unassociated with frank mycotic infections. The cases of atrophic vulvitis and those associated with secondary lichenification showed excellent anatomic as well as symptomatic effects. In the aged patient the skin, especially that of the vulva, undergoes atrophic changes which in turn reduce the normal excretion of fatty acids of the skin. The marked reduction or the absence of the fatty acids probably produces skin changes which may be associated with pruritus. The application of the propionates in a suitable ointment base relieves the pruritus and the skin regains the appearance of a more normal structure. The dryness, scaling, and waxiness disappear and the skin turgor is greatly improved.

There are certain cases of pruritus vulvae which do not respond to local treatment. There are patients who complain of severe symptoms and demonstrate neither visible skin changes nor evidence of scratching. Others in this same category complain only of severe burning. These two groups of patients may well fall into a true psychogenic class and will require careful psychiatric evaluation and treatment.

Recent investigations have indicated that the cutaneous secretory glands (sweat and sebaceous) produce protective substances which inhibit the growth of skin pathogens and saprophytes.<sup>3,4</sup> The odd chain fatty acids are apparently the most important antibiotics of the skin. The propionates are not only fungicidal but also bacteriostatic against the skin coeli.



Accordingly, the microscopic preparations from the Gynecologic Pathology Laboratory of Northwestern University Medical School of tissues from patients with carcinoma of the cervix have been examined. Ordinarily, only the cervical lesion is biopsied prior to the institution of radiation therapy. Consequently endometria were available in only eleven patients with carcinoma of the cervix. *Hyperplasia of the endometrium was found in only one of these eleven patients.* The findings in the remaining ten patients were as follows: early proliferative, 1; early secretory, 2; mid- or late secretory, 3; mixed proliferative and secretory, 1; typical postmenopausal (atrophic with areas resembling early proliferative), 1; and atrophic, 2. In ten of these eleven patients with cervical carcinoma, there was, therefore, no evidence of excessive endogenous estrogen as judged by the status of their endometria.

It is realized that this series is inadequate in itself, due to the relatively few endometria available. However, in two publications concerned with other aspects of cervical carcinoma, data on the status of the endometrium have been included. In 1923, Martzloff<sup>5</sup> studied the tissues from 387 patients with carcinoma of the cervix. The endometria were available in 208\* patients. Hyperplasia was present in only five, or 2.4 per cent.

More recently Pund and Auerbach<sup>6</sup> reported the endometrial findings in 39 patients with preinvasive carcinoma of the cervix. Hyperplasia was found in only two, or approximately 5 per cent. In the remainder, the findings were normal and varied with the menstrual cycle, postmenopausal, or pregnant status of the patient.

These combined data afford no evidence for the thesis that carcinoma of the cervix is caused by excessive estrogen stimulation. In fact, judging from the status of the endometria as reported by Pund and Auerbach and in our own data, ovarian function and hormone production in the vast majority of these women are essentially normal.

Before concluding, one other aspect of this subject should be mentioned. Reference is frequently made to the fact that prolonged administration of large amounts of estrogen causes carcinoma of the cervix in the experimental animal. The implication is made that this is true of all species in general. From this, it has seemed logical to assume that the same data apply to the human being. Actually carcinoma of the cervix has been produced with estrogen in only one species—the mouse.<sup>7</sup> It was claimed at one time that carcinoma of the cervix had been produced in the monkey, but the observed tissue changes were subsequently demonstrated to be only squamous metaplasia. Rats, rabbits, guinea pigs, monkeys and dogs have been given relatively tremendous doses of estrogens over long periods of time in various laboratories with no resultant cervical carcinoma. Since estrogen production of cervical carcinoma is limited to the one species, it is not logical to assume that results identical to those in this one species would necessarily be obtained in the human being.

\*Calculated from Martzloff's statement that hyperplasia was found in five patients who represented 2.4 per cent of those in whom endometria were available.

## EXCESSIVE ESTROGENS AND CERVICAL CARCINOMA\*

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IT HAS been claimed<sup>1</sup> and widely quoted<sup>2</sup> that vitamin B deficiency (thiamin and possibly riboflavin) may indirectly cause carcinoma of the uterus. The postulated mechanism is as follows: Normally the liver inactivates or destroys endogenous estrogens. With vitamin B deficiency, it loses this ability and the endogenous estrogens therefore become excessive in amount. The excessive estrogens in turn cause the carcinoma of the uterus.

In a later publication<sup>3</sup> the subject was limited specifically to carcinoma of the cervix. It was claimed that in 50 patients with carcinoma of the cervix evidence of excessive tissue estrogen was found in 92 per cent, as judged by cervical cornification smears, thiamine deficiency in 86 per cent, and riboflavin deficiency in 38.8 per cent. An additional factor favoring the estrogen-production of carcinoma theory was introduced. This was based on the belief that some degree of cervicitis is present in four out of five adult women. It was claimed that the infection in turn caused an increased concentration and fixation of estrogen in the cervical tissues and thus caused an even greater possibility of carcinoma of the cervix. This theory is based on experimental work in the rabbit by Brunelli.<sup>4</sup> He produced an acute hyperemic inflammatory reaction by local application of chloroform to the skin. His animals were then injected with estrogens intravenously and he was able to show estrogenic activity in extracts from the edematous hyperemic tissue, but not from control areas of the same animal treated locally with normal saline solution. He explained this by the known facts that circulating estrogens are bound to protein and that the tissue edema in such a reaction is due to transudation of proteins through the damaged blood-vessel walls. Part of the transudated protein carried bound estrogen with it.

There are no acute hyperemia and massive edema due to transudation of proteins in the chronically infected human cervix. The findings differ from those in Brunelli's rabbits. The assumption is, therefore, not warranted that there is also an increased local concentration of estrogens with chronic cervicitis.

If carcinoma of the cervix is caused by prolonged stimulation by excessive endogenous estrogen due to vitamin B deficiency, evidence of the effects of this excess should be demonstrable in other organs. It is commonly accepted that prolonged excessive estrogen stimulation causes hyperplasia of the endometrium. One would naturally expect, then, to find hyperplasia of the endometrium in patients with cervical carcinoma. The absence of hyperplasia would decrease the credibility of the estrogen theory of causation.

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# THE EFFECT OF STILBESTROL ON THE HEMATOPOIETIC SYSTEM IN THE HUMAN SUBJECT

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SHUTE<sup>21</sup> states that women who have prolonged bleeding and coagulation time usually have high blood estrogen. He concluded that stilbestrol might lower the platelet count and cause purpura and some damage.

Herbst<sup>10</sup> observed purpura in two men; Elias and Schwimmer<sup>3</sup> and Seligman<sup>19</sup> demonstrated distinct allergic reaction to stilbestrol and believe the reaction was due to hepatocellular impairment. Jaundice in these patients was of short duration and the recovery was complete. Loftis<sup>22</sup> also reported one case of purpura after a patient received estrogen. Von Haam and associates<sup>23</sup> observed an early mild decrease in platelet count but no purpura developed. Chevalier and Umdenstock<sup>5</sup> reported a fatal case of myelophthisis in a patient who received natural estrogen, not stilbestrol, over ten years for pruritus vulvae. Watson and co-workers<sup>26</sup> reported five cases of purpura due to natural or synthetic estrogen. Skin tests revealed definite skin sensitivity to estrogen.

Shorr and co-workers,<sup>20</sup> Davis,<sup>7</sup> Davis and Boynton<sup>8</sup> and the author<sup>12, 13, 14</sup> have made careful studies of the blood in a large series of patients receiving stilbestrol in doses of 1 to 5 mg. daily. These results revealed no abnormal changes and no tendency to purpura as suggested by Shute.<sup>21</sup>

It has been shown that dogs and rats are markedly affected, while monkeys are very slightly affected by even huge doses of stilbestrol.<sup>1, 2, 3, 4, 6, 11, 16, 18, 22, 23, 24</sup>

It was thought that a study of some of the formed elements of the blood in human beings should be reported, because stilbestrol is reasonable in cost and is now prescribed by many physicians. There is no report of the hemato-poietic system in human beings when large and unphysiological doses of stilbestrol were administered.

## Methods

A series of 65 patients, both pregnant and nonpregnant, were chosen from the Menstrual Disorder Clinic, Jefferson Davis Hospital, and were given various dosages of stilbestrol\* by mouth and intramuscularly for periods varying from one week to two years or more. The dose was increased every fourth night, one week, or two weeks. The largest daily dose of stilbestrol taken was 11,750 mg. and the smallest daily dose was 0.125 mg.

The following laboratory tests were made before, during, and after stilbestrol was administered intramuscularly and by mouth: bleeding and coagulation times, red and white cell count, hemoglobin, sedimentation rate, cholesterol, chlorides, uric acid, calcium, phosphate and fasting glucose.

\*Stilbestrol supplied by the Grant Chemical Co., N. Y.

### Summary and Conclusions

It has been theorized that there is an increased local concentration and fixation of estrogen in the chronically infected human cervix. This theory is based on experimental evidence in the rabbit. The pathologic findings in the chronically infected human cervix do not include the conditions necessary for an increased local concentration of estrogen in the rabbit's subcutaneous tissues. The theory is, therefore, not tenable.

It has also been postulated that carcinoma of the cervix is caused by excessive amounts of endogenous estrogens. The validity of this hypothesis was tested by examining the endometria from patients with carcinoma of the cervix. Excessive amounts of estrogen should cause hyperplasia of the endometrium. The incidence of hyperplasia was very low in this and in other reported series. This fact diminishes the credibility of the hypothesis.

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## Conclusions

In these series of human beings, the blood picture was not altered from the control, even when a total dosage of 181,960 mg. of stilbestrol was given to one patient over a period of less than one year.

No case of purpura or serious toxicity has been encountered in these series of patients or any other patient during the past ten years of stilbestrol studies.

No patient developed purpura hemorrhagica.

We might fairly conclude that stilbestrol produces little or no change in the hematopoietic system in human beings when doses recommended in the literature are given. The platelet count was approximately the same with or without stilbestrol, regardless of the dose.

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## UTERINE CULTURE TECHNIQUE

### A Simple Method for Avoiding Contamination by Cervical and Vaginal Flora

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IN THE course of an investigation concerning the bacterial flora of the post-partum uterus as affected by penicillin therapy, the usual techniques employed in obtaining material from the uterine cavity were found to be unsatisfactory. In the past, comparable investigations have been carried out, using either the Little tube<sup>1, 2</sup> or the sterile swab technique.<sup>3</sup> The method to be reported here has proved to be more satisfactory in avoiding vaginal and cervical contamination.

The initial uterine cultures in our series were taken with a Little tube on patients receiving intramuscular penicillin therapy, and showed numerous contaminants. Subsequent cultures taken with our new technique on a similar group of patients yielded a large majority of sterile cultures. Cultures on a control group of patients receiving no penicillin showed predominantly anaerobic streptococci and *Bacteroides*, with only occasional coliform bacilli, staphylococci, or other organisms which might be regarded as possible contaminants. The complete results of our investigation with the employment of this method will be reported subsequently. The purpose of this paper is simply to describe the technique used in taking the uterine cultures.

### Equipment

The instrument used in obtaining material from the uterine cavity consists of: (1) a stainless steel or chrome-plated tube 12 inches in length with a  $\frac{1}{4}$ -inch bore, curved on one end; (2) a sharp steel stylet which projects very slightly beyond the end of the metal tube when inserted; (3) a steel wire with a small loop on one end which will project  $\frac{1}{4}$  inch beyond the end of the tubing and through the loop of which a small piece of cloth (i.e. cord tie) may be tied. These are sterilized by autoclaving along with a gauze sponge on a clamp and several 6-inch pieces of braided silk cord.

As will be described, rubber finger cots are used to protect the tip of the metal tube from cervical contamination while being inserted into the uterus. These finger cots are unrolled and sterilized by soaking in an aqueous Zephiran solution 1:1,000 for forty-eight hours. They are dried immediately before using. Repeated tests have shown finger cots treated in this manner to be sterile, and it has been demonstrated that no disinfectant is carried over into the culture medium to inhibit the growth of any organisms which may be present. Heat sterilization and other chemical methods were found to give incomplete sterilization, or to affect the elasticity of the rubber.

Other equipment used in taking the uterine cultures includes sterile gloves, a sterile bivalve speculum and tubes of thioglycollate medium for inoculation (Fig. 1).

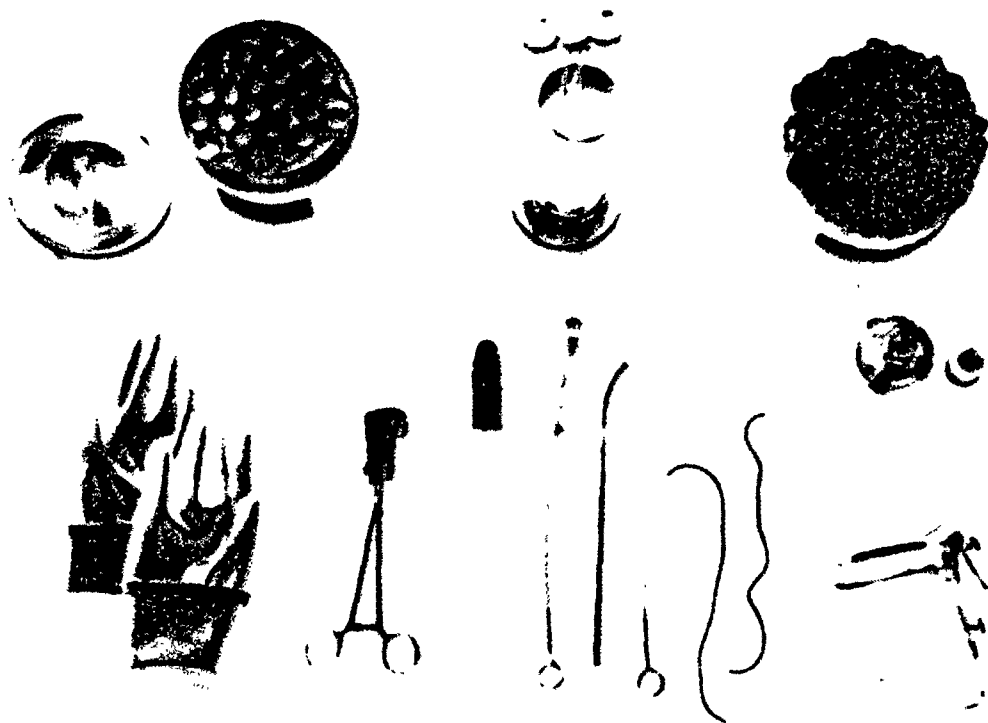


Fig. 1.—Actual photograph of equipment used for taking uterine cultures.

### Procedure

The patient is placed in dorsal lithotomy position and draped in the conventional manner. A sterile bivalve speculum is introduced into the vagina and the cervix is visualized. Blood clots and/or products of conception are gently removed from the cervix with a sterile sponge. Sterile gloves are then donned and a sterile, dry finger cot is drawn taut over the tubing and tied in place. The tube is then inserted through the cervical canal and past the internal os for a centimeter or so in order to be past the bacterial flora of the vaginal and cervical canals (Fig. 2). The sharp stylet is then introduced into the tube and the rubber closing the tip of the tube is pierced. The taut rubber retracts instantaneously on the tubing, leaving a sterile end, uncontaminated by vaginal or cervical flora. The stylet is removed and the wire loop containing the wick is introduced through the tube. The tube is then advanced several centimeters more into the uterus and the wire loop is twisted from side to side in the uterine cavity in order to collect sufficient material on the wick (Fig. 3). The wire loop is then withdrawn, leaving the tubing still in place, and the material collected on the wick is implanted in thioglycollate medium. Finally, the tube is removed. Definite evidence that sufficient material for culture is obtained is revealed by a serosanguineous soaked wick, which frequently has blood clots adhering to it.

Using this procedure, we have caused no apparent morbidity from carrying bacteria into the uterine cavity, and have seen no endometritis or injury resulting from the technique.

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### Summary

A simple technique for collecting material from the uterine cavity for bacteriologic examination is described. The method has the advantage of avoiding contamination of the culture by cervical or vaginal flora.

The authors wish to acknowledge their indebtedness to Dr. Conrad G. Collins, Professor of Obstetrics and Gynecology, Tulane University School of Medicine, who first suggested to one of them (J. A. G.) the idea upon which the technique described is based.

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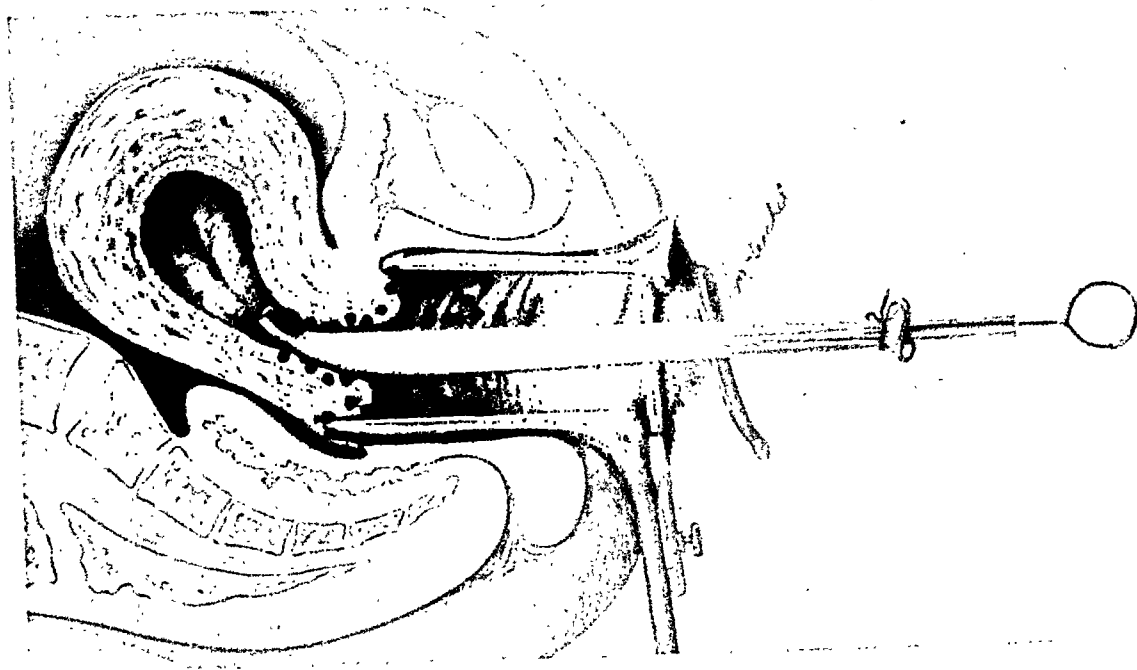


Fig. 2.—Diagrammatic cross section showing culture tube through cervix beyond the internal os. Finger cot has been drawn taut and the stylet partially inserted preparatory to perforating the stretched rubber protecting the end of the metal tube. Vaginal and cervical flora indicated by dots.

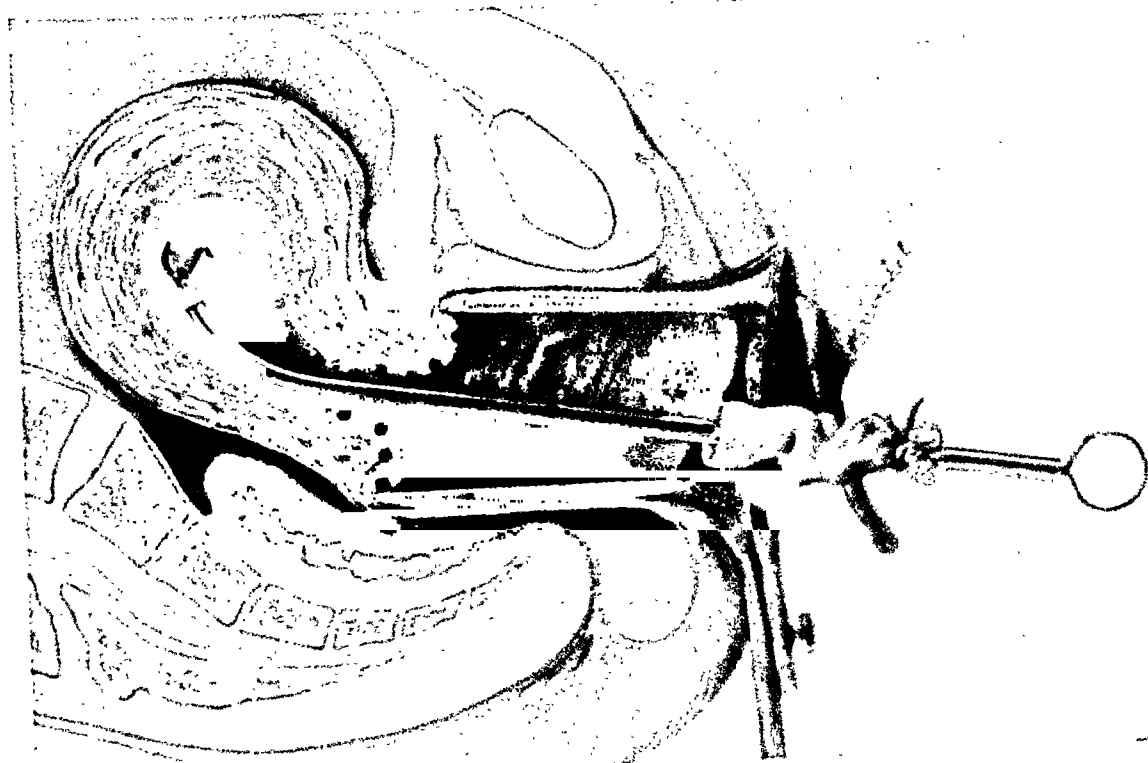


Fig. 3.—Diagrammatic cross section revealing wire loop in place following perforation and retraction of the finger cot which is shown retracted into the vagina. A culture with vaginal and cervical flora is avoided and a culture representing the true uterine flora is thus obtained.

Early in 1931, Dr. Perry W. Ross, an intern at the Cook County Hospital and thus much more interested in the cancer diagnostic problem, happened to see me make some laboratory measurements on animal tumors. He persuaded me to set up the potentiometer in his ward at the County Hospital and together we made measurements on accessible tumors in patients. The differences in electronegativity between benign and malignant tumors seemed conclusive. Dr. Fred Falls, Chief of the Gynecologic Division of the hospital, had us do some measurements in his presence. These were all in patients with lesions of the cervix, which, after speculum visualization, had inserted into it one-half to one inch of platinum wire, 22 gauge, as the "different" electrode. The indifferent electrode was a saturated KCl-mercurous chloride half-cell, in contact with any portion of the patient's skin; just where, appeared to be immaterial. The potential was recorded by null-point using a light beam galvanometer. No special provision was made to shield from electrical fields, or to insulate any patient who was placed either on the ordinary metal hospital bed or metal examining table. I suppose the electrical fields mentioned by Drs. Langman and Burr as to be avoided were those in any large hospital with a busy elevator, x-ray and diathermy service. These seemed to lend no interference or else the simplicity and ruggedness of our apparatus permitted dispensing with those precautions emphasized by later writers. In any event, Dr. Falls considered those measurements which he witnessed to be of diagnostic import. What may have convinced him was the instance of one patient in whom he thought we were certainly measuring the potential of a submucous uterine fibroid, which, to our consternation, evinced a marked electronegativity. The tumor turned out to be an adenocarcinoma.

Through the good offices of Dr. Hektoen, Dr. Paul R. Cannon, then President of the Chicago Pathologic Society, was apprised of our work and Dr. Cannon sponsored our appearance before that society for presentation of a preliminary report. While I was still chary of claiming a diagnostic aid, holding that anything that could be reached by an electrode would be accessible for punch or needle biopsy, my co-worker, Dr. Ross, had his say in the presentation because the latter paragraph of the abstract (*Arch. Path.* 15: 169, 1933) reads:

"Potentiometric measurements were made of human tissues from four sources: ulcerating malignant tumors in situ, ulcerating non-malignant growths in situ, excised malignant tumors and excised non-malignant tissues. The average potentials for the malignant tissues were significantly more electronegative than those exhibited by others. An analysis of the data secured by potentiometric measurement of ulcerative conditions in situ indicates that such results may have some diagnostic value."

A definitive paper incorporating the data presented to the Society was submitted to the *American Journal of Cancer* and rejected on the basis of the question of validity, though, early in 1933, I had demonstrated to the editor of this journal, Dr. Francis Carter Wood, in his own laboratory, on tumors from his own colonies and with a potentiometer setup extemporized from his own laboratory equipment, the extreme relative electronegativity of tumor tissue. Representative data from the Society presentation, incorporated in the rejected paper, are shown because of the interesting correlation with the work of Dr. Langman and Dr. Burr.

These data indicate that the electronegativity exhibited by malignant tissues does not restrict itself to those originating in the cervix uteri, but may be a generalizing property of a number of tumors whose malignancy is contingent on invasiveness. Not indicated by these data are measurements made subsequent to their procurement and submission, in which the platinum electrode was plunged through intact tissue into a subjacent tumor, where, when the latter was malignant, the decisive electronegativity was registered in a number of instances. That the greater potential will be recorded under these circumstances, follows from theoretic considerations also, potential being an intensity factor. It appears on a practical basis that the electronegative "current of injury" of benign tissue does not have as high an intensity factor as that originating from malignant tissue; when both benign and malignant tissues are simultaneously in contact with the same electrode, that of the malignant tissue appears to take precedence just as when two electromotive batteries of different voltage are placed in parallel, a voltmeter will indicate the voltage of that which has the higher intensity factor. These considerations, both theoretical and practical, lend further promise to the evolution of a diagnostic procedure whatever the location of the tumor.

PLATINUM ELECTRODE POTENTIALS ON SATURATED KCl-CALOMEL SCALE OF  
HUMAN TISSUES IN SITU

<i>I. Histologically Malignant Conditions</i>	<i>Location</i>	<i>Potential in mv.</i>
1. Adenocarcinoma	Breast	-.268
2. Adenocarcinoma	Breast	-.205
3. Adenocarcinoma	Breast	-.197
4. Adenocarcinoma	Breast	-.215
5. Adenocarcinoma (scirrhus)	Breast	-.220
6. Carcinoma	Cervix	-.296
7. Carcinoma	Cervix	-.217
8. Carcinoma	Cervix	-.215
9. Carcinoma	Cervix	-.299
10. Carcinoma	Fundus uteri	-.242
11. Squamous cell carcinoma	Vulva	-.212
12. Colloid carcinoma	Rectum	-.189
13. Adenocarcinoma	Prostate	-.211
14. Malignant melanoma	Axilla	-.238
15. Malignant melanoma	Chin	-.242
16. Osteosarcoma	Humerus	-.373
17. Osteosarcoma	Tibia (solid tumor) (necrotic portion)	-.282 -.387
18. Squamous cell carcinoma	Penis	-.254
19. Adenocarcinoma of cecum	Abdominal wall (solid tumor) (necrotic portion)	-.282 -.370
20. Adenocarcinoma of stomach	Supraclavicular gland	-.245
<i>II. Histologically nonmalignant conditions</i>		
1. Tuberculous osteomyelitis	Ilium	-.118
2. Tuberculous osteomyelitis	Femur	-.081
3. Tuberculous osteomyelitis	Vertebra	-.116
4. Tuberculous fistula	Anus	-.078
5. Tuberculous fistula	Anus	-.165
6. Tuberculous fistula	Anus	-.108
7. Tuberculous fistula	Anus	-.071
8. Tuberculous fistula	Abdominal wall	-.164
9. Tuberculous fistula	Abdominal wall	-.069
10. Plantar wart	Foot	-.084
11. Giant-cell tumor	Fibula	-.121
12. Erosion	Cervix	-.112
13. Erosion	Cervix	-.120
14. Erosion	Cervix	-.116
15. Erosion	Cervix	-.106
16. Cervicitis (subacute puerperal)		-.162
17. Cervicitis		-.141
18. Cervicitis		-.223
19. Cervix (normal)		-.098
20. Granulating wound, postappendectomy	Abdominal wall	-.178
21. Varicose ulcer	Leg	-.170
22. Pericanalicular cystadenoma	Breast	-.132
23. Chronic cystic mastitis		-.108

In drawing any comparison, one must take into account our use of the saturated KCl-mercurous chloride cell as a reference indifferent electrode and platinum as the "different" one; our reference scale of "negativity" is thereby shifted from the position of that occupied when using silver chloride as both electrodes. Drs. Langman and Burr thus automatically set their skin potential, as a reference point, at zero but this, like "positivity" and "negativity," is purely relative. For practical purposes, the earth may be considered to be at zero potential but it is electronegative to cloud banks on some occasions and electropositive on others; this governs the direction in which lightning may leap, after which clouds and earth are electrically neutral toward each other. Had we chosen the hydrogen electrode as a reference half-cell, all our potentials would be markedly different but would still exhibit the differential; with the employment of a half-cell with an intrinsic potential just 180 mv. more electropositive than the saturated KCl-calomel, the signs on most of the nonmalignant tumor potentials would appear positive and the parallelism between our data and that of Drs. Langman and Burr, more striking. As it happens, the only other comparable data

in the literature is that of Dr. E. Sorn (*Compt. rend. Soc. de biol.* 108: 327, 1931) who independently measured what he thought to be oxidation reduction potentials in animal tumors, by a technique and with results practically identical with our own on such tumors.

That I was exceedingly remiss in not presenting the matter solely on the discouragement of having a single paper rejected by a single journal, is freely admitted and apologies are in order to Drs. Hektoen, Ross, and Cannon who gave their active encouragement and help. When, later, I went into clinical medicine, I could find no justification for an ivory tower seance of the cancer problem. The original study may ultimately turn out not to have been a total loss for there have been certain philosophic outgrowths that may result in some salvage.

The electronegativity of some cancer cells, if truly contingent upon an increased degree of dispersion of the nucleoplasm of such cells, has already explained their hyperchromia to hematoxylin staining. It may likewise explain their propensity for irregular karyokinesis or akaryokinesis, the nucleus tending to tear apart through the agency of increased mutual repulsion between hyperelectronegative aggregates comprising it, just as the vanes of a gold-leaf electroscope will tear from their support when an excessive charge is imposed. The relative radiosensitivity of these cancer cells may be explained on the same basis. Penetrating radiant energy or subatomic particles may neutralize such excessive charges by the same mechanism as they will cause the discharge of the vanes of an electroscope.

Hope for a new approach to chemotherapy of cancer is also afforded on this hypothesis. If a relatively electropositive colloid could reach the malignant cells, their aberrant charge might be neutralized. Our cited examples of hematoxylin and methyl green are not suitable since the plasma proteins are relatively electronegative to them and mutual colloid precipitation would take place in the blood stream. What is needed is an electrically inert substance which, in the vicinity of the differentially electronegative tumor cell, would be converted to, or would yield a relatively electropositive colloid. It was for this purpose that the metalloferrihemoglobins were prepared from waste human erythrocytes (*J. Am. Pharm. A.* 35: 165, 1945).

The latter compounds, though known for several years, have never interested those agencies engaged in experimental cancer therapy. Nothing lacked in the chemical reasoning involved but none were satisfied that the differential electronegativity of cancer tissue had been established. From this standpoint as well as many others, the report of Drs. Langman and Burr may be most timely.

ROBERT D. BARNARD, M.D.

565 FIRST STREET  
BROOKLYN, N. Y.  
MAY 11, 1949

### Reply by Drs. Langman and Burr

To the Editor:

In reply to Dr. Barnard's communication, we would like to say that we were glad to learn of findings similar to ours with other techniques.

We had not been aware of his work and did not find any reference to the publication mentioned in his letter in our search of the literature. It shall be included in our bibliography.

We appreciate the references in his letter and are glad for the opportunity to learn of his observations.

HAROLD S. BURR, PH.D.  
LOUIS LANGMAN, M.D.

940 PARK AVENUE  
NEW YORK, N. Y.  
MAY 18, 1949

# Item

## Diplomates

Candidates certified at annual meeting and examinations, American Board of Obstetrics and Gynecology, Inc., May 8 to 14, 1949:

Adler, Samuel Sidney	229 Broad Street	Red Bank, New Jersey
Allan, Malcolm Stuart	127 Maple Street	Springfield, Massachusetts
Altimas, Gerald Thos.	1374 Sherbrooke Street, W.	Montreal, Quebec, Canada
Andries, George Henry	853 Fisher Building	Detroit 2, Michigan
Andros, George James	5841 South Maryland Avenue	Chicago 37, Illinois
Atherton, Hazel Earl	1428 Madison Avenue	Memphis, Tennessee
Baer, Raymond B.	7815 East Jefferson Avenue	Detroit 14, Michigan
Bailey, Harmon J.	23 Flint Street	Asheville, North Carolina
Baker, J. Tyler	214 Dover Street	Easton, Maryland
Baldwin, Auburn Lewis	401 Highland Building	Pittsburgh, Pennsylvania
Ball, Orrie H.	426 Unity Building	Bloomington, Illinois
Barnett, Stephen T., Jr.	26 Linden Avenue, N. E.	Atlanta, Georgia
Barney, Azel Packard	127 Maple Street	Springfield 5, Massachusetts
Barter, Robert H.	Gallinger Municipal Hosp.	Washington 3, D. C.
Bellville, Titus P.	1409 Willow Street	Minneapolis 14, Minnesota
Benschine, Frederick W.	57-02 142nd Street	Flushing, L. I., New York
Benson, Seymour	4418 Vineland Avenue	North Hollywood, California
Bergin, Paul Francis	117 Coolidge Road	Worcester, Massachusetts
Bischoff, Theodore M.	Mayer Building	Portland 5, Oregon
Block, Nathan	25 Oak Grove Drive	Baltimore 20, Maryland
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Eastman, Oliver Rolfe  
Elvin, Arthur G.  
Esslinger, Arthur T.  
Evans, William Ward  
Fagin, Joseph  
Felmus, Laurence Bruce  
Ferguson, James Henry  
Fetterhoff, Charles K.  
Finn, William Francis  
Flynn, Simon A.  
Forman, Richard C.  
Forman, Simon B.

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Frankel, Donald S.  
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Fulmer, George T.  
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Garrison, Geo. H. H.  
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Goldstein, Louis  
Greenstein, Carl  
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Hurter, Andrew Jerome  
Igna, Eli John  
Imerman, Harold M.  
Jacobs, Ralph I.

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Jones, John Walter  
Kacher, Leon  
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530 East 70th Street  
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2005 Pine Street  
853 Fisher Building  
2118 Pine Street  
5841 Maryland Avenue  
2535 31st Avenue  
490 Post Street  
39 North Goodman Street  
113 West Monument Street  
1007 Park Place  
1229 Park Road, N. W.  
3209 North Meridian Street  
45 Plaza Street  
141 West 109th Street  
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85 Trumbull Street  
2529 Pennsylvania Ave., N.W.  
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1101 Beacon Street  
211 Lexington Avenue  
121 University Place  
1024 Ocean Avenue  
431 Thirtieth Street  
269 South 19th Street  
16 Hampton Village Plaza  
164 Division  
2000 Santa Clara Avenue  
384 Redondo Avenue  
1093 Beacon Street  
N.E. Cor. 10th & Lindley Ave.  
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5051 Oxford Avenue  
9 Lafayette Avenue  
1441 East 26th Street  
Medical Arts Building  
602 West University Avenue  
673 Fisher Building  
416 North Bedford Drive  
Sequoia Medical Group, 90  
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296 South Goodman Street  
205 West Main Street  
401 East Fifth Street  
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Dallas 4, Texas  
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Philadelphia 3, Pennsylvania  
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Brooklyn, New York  
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Chicago, Illinois  
Canton 2, Ohio  
Springfield, Massachusetts  
Wenatchee, Washington

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		Philadelphia 17, Pa.



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Skiles, James Hubert, Jr.	715 Lake Street	Oak Park, Illinois
Slovin, Isadore	1101 North Jackson Street	Wilmington, Delaware
Smatko, Andrew John	416 North Bedford Drive	Beverly Hills, California
Smith, George Edwin	318 South Washington Street	Royal Oak, Michigan
Smith, Hugh R.	430-436 University Club Bldg.	St. Louis 3, Missouri
Smith, Stedman W.	500 North Division Street	Salisbury, Maryland
Snyder, Charles Travers	17 West 54th Street	New York 19, New York
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Speck, George	2808 South Randolph Street	Arlington, Virginia
Spencer, John A.	490 Post Street	San Francisco 2, California
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Thornton, John Joseph	270 Commonwealth Avenue	Boston, Massachusetts
Thron, Leopold Edward	586 East 29th Street	Paterson 4, New Jersey
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Tripp, Louis A.	511 Lafayette Avenue	Buffalo 14, New York
Van Ness, Albert Ward	400 Medical Arts Building	Syracuse, New York
Warm, Herbert	508 First National Bank Bldg.	Hamilton, Ohio
Weinberg, Carl Herman	502-503 Medical Arts Bldg.	New Orleans, Louisiana
Wenger, Christian S.	236 North Duke Street	Lancaster, Pennsylvania
Wentsler, Norman E.	1029 Second Nat'l Bldg.	Akron 8, Ohio
Werner, Irving	112 Murray Street	Binghamton, New York
Wilhelm, Emanuel C.	438 West Front Street	Traverse City, Michigan
Williams, Ben C.	3500 East 17th Avenue	Denver 6, Colorado
Wilson, James A.	1611 Sonoma Street	Vallejo, California
Wilson, Thomas Reid	602 West University Avenue	Urbana, Illinois
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Worden, Robert W.	415 Pujo Street	Lake Charles, Louisiana
Zakin, David	1100 Park Avenue	New York 28, New York
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Zimmermann, Edward A.	Box 0, Ancon, Gorgas Hosp.	Panama Canal Zone

### Erratum

In the article, "The Effect of *Veratrum Viride* on the Urine Volume, Blood Pressure and Pulse Rate in Normal and Toxemic Pregnancy," by N. S. Assali, R. W. Kistner, and S. T. Garber, in the July issue of the JOURNAL, on page 99, line 19, the word "hemostasis" should be "homeostasis." The sentence should read, "It can possibly be explained by a relative and transitory homeostasis due to a sudden fall in blood pressure aggravated by the vomiting and profuse diaphoresis."

Keys, Edgar Hayden, Jr.  
Kilkenny, George S.  
Knowles, Edward Taylor  
Lach, Frank Edward  
LaMariana, Peter  
Lage, George Hans  
Lambert, Warren Chas.  
Laughlin, K. Alexander  
Lobraico, Rocco V., Jr.  
Longyear, Harold W.  
Lusk, Harry Arnold  
Macatee, George, Jr.  
MacDonald, J. Kingsley  
Maeck, John V. S.  
Maier, Reuben Ralph  
Maloney, Francis D.  
Marenius, Edward B.  
Marshall, Jennings B.  
Martinak, Richard E.  
Martini, Arthur P.

Mason, Vaughan C.  
Meister, Peter Carl  
Mellow, Joseph A.  
Mendel, Evri Bear  
Merk, Harvey John  
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Miller, Max Mayo  
Mitchell, Bruce B.  
Mitchell, George John  
Morgan, James Edward  
Murrieta, Alfred J., Jr.  
Mussey, Mary Elizabeth  
Myller, Ernest  
McAllister, John Edw.  
McCloskey, Richard C.  
McCorriston, Colin C.

McFadyen, Elmer H.  
McGill, John Francis  
McRoberts, William A., Jr.  
Nace, Fay Morris  
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Neimand, Karl M.  
Nelson, Robert B., Jr.  
Noble, Vernon A.  
O'Hare, John F.

Ostrom, Eugene W.  
Paalman, Russell J.  
Padgett, H. O.  
Pagano, Alphonse F.  
Parker, Joseph C.  
Parrott, Max Horton  
Pedowitz, Paul  
Pollack, Samuel Louis  
Porreca, George A.  
Posey, Frank M., Jr.  
Potter, Charles  
Reishtein, William A.  
Riva, Humbert L.  
Rivers, Arthur Lee  
Rizika, Stuart David  
Roe, Isabel Roberts  
Rosen, Bernice Shirley  
Rothman, Albert  
Rucker, John Collier

1101 Maine Street  
709 North 11th Street  
U. S. Naval Hospital  
59 Trumbull Street  
59 Broad Street  
550 Medical Arts Building  
111 South Front Street  
201 State Street  
30 North Michigan Avenue  
706 Maccabees Building  
947 West 8th Street  
610 City Building  
1524 Harding Place  
24 Clarke Street  
10515 Carnegie Avenue  
176 Fulton Avenue  
255 South 17th Street  
609 Brown Building  
1528 Medical Arts Building  
Pent House, Eugene Medical  
Center

545 West 148th Street  
232 Russo Building  
12 Bernard Street  
3524 Fairmont Street  
30 Pierrepont Street  
320 North Main Street  
220 Foster Street  
920 Heyburn Building  
461 Government Street  
4169 Pearl Road  
635 South Westlake Avenue  
Mayo Clinic  
875 Park Avenue  
210 Medical Arts Building  
7115 Thomas Blvd.  
The Clinic, 881 South Hotel  
Street

303 MacMillan Building  
1933 Pacific Avenue  
904 Holman Street  
1312 Medical Arts Building  
125 Maple Street  
55 E. Washington Street  
652 Eastern Parkway  
1824 Massachusetts Ave., N.W.  
718 National Bank Building  
Permanente Foundation Hosp.  
280 MacArthur Blvd., W.  
4013 North Milwaukee Avenue  
1144 Madison Ave., S.E.

544 78th Street  
1001 West Franklin Street  
508 Medical Arts Building  
589 Eastern Parkway  
110 Avenue des Braves  
1843 South Broad Street  
640 New Moore Building  
223 Thayer Street  
16 Blancoyd Road  
Walter Reed General Hosp.  
231 Calhoun Street  
420 Medical Arts Building  
2201 St. James Place  
8 South Michigan Avenue  
3952 West Jackson Blvd.  
Travis Clinic, Travis Bldg.

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the Fallopian tubes and ovaries. Helwig reported thirty cases in 1925. In 1934 the number had risen to seventy-two, as reported by Cornell. We found thirty-seven more cases in the literature up to 1946. These have been added to this study, bringing the total to one hundred nine.

### Materials and Methods, Present Study

This study is based on the literature and on eight cases from the files of the Mayo Clinic. A summary has been made of all cases reported up to Jan. 1, 1946. Our eight cases are reported in detail, with special reference to the pathology, treatment, and prognosis.

The statistical results compiled in a study of the cases in the literature and of our cases are analyzed separately and compared. Emphasis is placed on the diagnostic and therapeutic measures used in this disease to show how they have changed in the past decade.

### Pathogenesis

The causative organism of actinomycosis is a delicate, thermolabile, anaerobic fungus which has been given the name *Actinomyces bovis*. This is the organism of Wolff and Israel, and its specificity has been definitely proved. *Actinomyces bovis* also causes lumpy jaw in cattle. Actinomycosis is found the world over; there is no evidence of endemicity. In the United States, Sanford found the disease especially prevalent in the upper Mississippi River valley and the north-west region.

In 80 per cent of cases the disease occurs in young adult persons. Occupation seems to have no influence on it. Macnab wrote that there is little evidence that the disease can be transmitted directly from man to animal or from animal to man. Contagion from man to man never has been established.

There are two views as to the mode of entry of the organism:

*Exogenous Route.*—Supporters of this theory cite the cases in which a history of the chewing of raw grain or grasses has been elicited. There are also cases in which barbs of grain have been found in the actinomycotic lesions. These factors constitute circumstantial evidence that the chewing of grasses and grains may predispose the victim to the disease.

*Endogenous Route.*—The bulk of evidence indicates that Actinomyces are normal inhabitants of the mouth and intestinal tract. Slack isolated anaerobic Actinomyces from fourteen of one hundred tonsils removed consecutively, and from eighteen of one hundred samples of pus from persons with pyorrhea. Emmons found Actinomyces-bearing granules in forty-seven of one hundred pairs of tonsils. Weller found eight instances of tonsillar concretions in 1,000 tonsils; forty-seven of these eighty were composed of Actinomyces-like colonies of mixed organisms.

The organism is an anaerobic fungus, difficult to grow. It has not been isolated from grasses and grains. It probably cannot invade tissue except under favorable circumstances. Minor trauma is thought to be necessary to give the organism a portal of entry.

*Portal of Entry in Actinomycosis of Fallopian Tubes and Ovaries.*—The intestinal tract probably is the prime seat of infection. In most cases the disease is thought to have this origin, even though a lesion in the bowel is demonstrated rarely. Failure to demonstrate a macroscopic or a microscopic lesion in the intestine adjacent to the ovarian mass has been variously explained. First, Brickner felt that the organism could pass through the gut wall without producing a lesion therein. Second, it may be that there is a primary lesion in the wall of the bowel, but if so, such a lesion might be healed by the time the disease is manifest in the tubes and ovaries, since mucous membrane is known to

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## ACTINOMYCOSIS OF THE OVARIES AND FALLOPIAN TUBES\*

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ACTINOMYCOSIS of the ovaries and Fallopian tubes is one of the less common diseases confronting the gynecologist. Since, however, there are more than one hundred reports of cases of this condition in the literature, every gynecologist who treats so-called pelvic inflammatory disease should be aware of the possibility of infection with Actinomyces.

In the past, the outcome of this disease when it affects the female internal genitals has not been encouraging. The advent of chemotherapy has markedly changed the prognosis. There have been no extensive studies of the problem since sulfonamide compounds and penicillin came into general use. Hence, it was thought that a comprehensive study would be of benefit to those who are likely to be confronted with pelvic actinomycosis.

### Antecedent Studies

According to Gardiner and Welsh, the credit for the discovery of Actinomyces goes to Laugenbeck, who found "sulfur granules" in the jaw lesions of cattle in 1845. According to Wright, Harz in 1877 suggested the name "ray fungus" or "Actinomyces bovis."

Rosebury<sup>26</sup> stated that Wolff and Israel in 1891 were the first to obtain pure cultures of the organism.

Numerous cases of actinomycosis were reported by 1905, but there were few concerning the internal female genitals. In 1909 Taylor and Fisher found only six cases. In 1919 Robinson could find only nineteen cases of actinomycosis of

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### Pathologic Aspects

*Gross Pathologic Aspects.*—As a rule, a granulomatous tubo-ovarian mass is seen adherent to surrounding structures. These masses vary from the size of a walnut to tumors filling the entire lower part of the abdomen. They are greenish white or yellowish, often mottled. They are soft, friable, fluctuant and

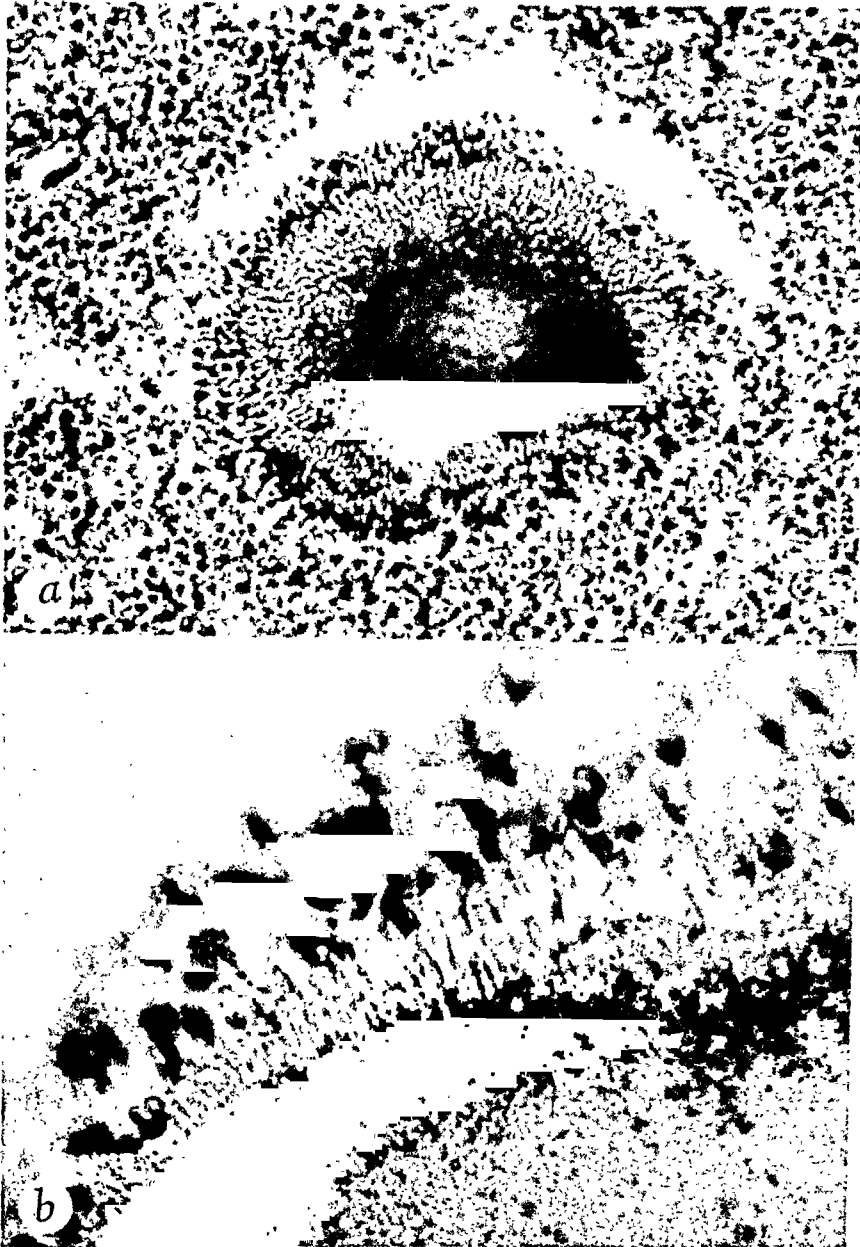


Fig. 1.—*a* (Case 7), Typical actinomycotic colony in section of an ovary (hematoxylin and eosin,  $\times 240$ ); *b* (Case 7), Detail of the peripheral club arrangement at the edge of a colony of actinomyces organisms (hematoxylin and eosin,  $\times 900$ ).

elastic, but occasionally may be hard. The surface may be smooth or roughened, but most often shows a moth-eaten appearance, with protrusions of various sizes and shapes. Pus may exude from the tumor.

be resistant to Actinomyces. Third, the disease may be spread by the help of other organisms. Fourth, it may be spread by the blood stream.

Gardiner and Welsh believed the ovaries are the chief sites of pelvic infection with this disease. The proximity of the right ovary to the appendix is said to be important, because the appendix is the commonest site of abdominal actinomycosis. The ovaries are thought to be favorable sites for the lodgment and growth of the organism, especially at the time of ovulation.

It is also possible for the organism to gain entry through the vagina. Tietze described a case in which the infection seemed definitely to follow the use of a pessary. De Faria and Fialho reported a case in which pelvic actinomycosis followed abortion attended by infection. Campbell and Greaves reported actinomycosis of the cervix uteri. Other authors<sup>8, 15, 18, 20, 23, 29, 33, 34</sup> have reported cases of actinomycosis that probably was primary in the pelvis.

The disease in the pelvis usually is restricted to the tubes and ovaries. The well-known resistance of the pelvic peritoneum and the tendency toward localization of infections in this area may account for the early seemingly benign course and protracted illness without more frequent evidence of early generalized peritonitis.

### Bacteriologic Aspects

There has been much confusion in the literature regarding a system of classification of Actinomyces. The general classification of Waksman and Henrici is used in describing the fungi-producing true mycelia.

*Actinomycetaceae*.—These are organisms in which the mycelium fragments into bacillary or coccoid elements. These may be subdivided into Actinomyces and Nocardia.

*Actinomyces*.—Members of the genus Actinomyces are anaerobic or microaerophilic, parasitic, and not acid-fast. They are found in the alimentary tract of man and animals. They are gram-positive. In tissue they form "sulfur granules," which are cauliflower-shaped mycelial masses with radial-club arrangement at the periphery (Fig. 1, a). These clublike bodies (Fig. 1, b) are pear-shaped thickenings of the terminal filaments; they are hyaline, refringent, and vary in size and thickness. All transitions between the clubs and filaments may be present beneath the peripheral layer. On culture media they form bacteria-like colonies without aerial hyphae and they produce no spores or pigments. They grow best at body temperature. Their oxygen tolerance is very limited. They do not liquefy gelatin. The species is heterogenous and has not yet been satisfactorily subdivided. *Actinomyces bovis* or *Actinomyces israeli* is the best-known organism in this group. The term "actinomycosis" probably should be limited to lesions caused by this type.

*Nocardia*.—Members of the genus Nocardia are aerobic and partially acid-fast or are not acid-fast. They do not form spores. Species of Nocardia sometimes are pathogenic and may produce actinomycosis-like lesions in man.

*Streptomycetaceae*.—These are organisms in which the mycelium does not fragment. They are aerobic. They are found widely in nature in soils, manure, grasses, and grains. On culture, the colonies often produce aerial hyphae. They form highly specialized spores and various-colored pigments. These organisms grow best at 15° to 20° C. (59° to 68° F.). Many are actively proteolytic. They occasionally produce actinomycosis-like lesions in man. Streptomycetaceae may be divided into Streptomyces and Micromonospora.

*Streptomyces*.—Members of the genus Streptomyces multiply by the formation of conidia in chains from aerial hyphae.

*Micromonospora*.—Members of the genus Micromonospora multiply by the formation of single terminal spores on short sporophores.

uterus itself is rare, but the parametrium often is involved. There may be sinus tracts into the bowel, bladder, or skin.

*Microscopic Pathologic Aspects.*—The lesions begin as an accumulation of polymorphonuclear leucocytes about the organism; this process eventually results in liquefaction necrosis (Fig. 1, *a*). About this center is a zone of lymphocytes and plasma cells, interspersing a mass of endothelial-like cells. This is surrounded by a loose honeycomb layer of granulation tissue and fibrosis. There is always a tremendous fibroblastic reaction (Fig. 2, *a*). The blood vessels in the fibroblastic stroma are intact in comparison with the endarteritis associated with tuberculous or syphilitic infections (Fig. 2, *b*). Caseation necrosis is not seen, but giant cells occasionally are observed. Calcification is rare. Under low-power magnification, multiple small abscesses of the type described above are seen (Fig. 2, *a*). Some of the areas of infection may show numerous colonies of organisms, but generally it is necessary to search for even a single colony. Other areas with the same microscopic appearance show no colonies.

*Progress of the Lesions.*—Actinomyces spreads by direct extension or via the blood stream, rarely by the lymphatic route. The organism is said to be too large to be able to invade lymph channels. However, Draper and Studdiford reported one case in which the mesenteric lymph nodes were definitely involved with actinomyces.

Usually, the lesions progress peripherally, producing adhesions to, and abscesses of, contiguous structures. These eventually rupture spontaneously to the surface, with the formation of sinuses. This process may be the body's attempt at extrusion of the infecting organism, as it would extrude a foreign body. The organism is capable of invading bone as easily as soft tissue; actinomyces osteomyelitis is not uncommon. The free rupture of actinomyces abscesses occasionally produces generalized peritonitis.

### Clinical Course

*Clinical Characteristics.*—The early symptoms and course of actinomyces of the internal female pelvic organs are not characteristic. In the early stages the disease simulates pelvic inflammatory disease of other causation, and, when it is more acute, it may resemble appendicitis. Seven of our eight patients gave a history of pain in the lower part of the abdomen, usually located on one side, at the onset of their illness. The remaining patient had had symptoms of partial obstruction of the bowel for which colostomy had been done. Six of the eight patients had associated fever; three experienced vomiting with their attacks. Only one patient (Case 3<sup>e</sup>) had noticed any swelling in the abdomen.

It is interesting to note that all eight patients had undergone surgical treatment elsewhere. In only one instance (Case 6) had actinomyces been diagnosed prior to entry of the patients at the Mayo Clinic. Previous surgical treatment varied: six had undergone gynecologic operations; four of them had had some portion of the pelvic organs removed; one had undergone colpotomy; one had undergone a simple exploratory operation. Of the other two patients, one had undergone simple incision of an abdominal abscess; for the other, colostomy had been performed for partial obstruction of the bowel.

Ages of the patients ranged from 23 to 46 years, with an average of 34.4 years.

The duration of symptoms prior to entry of the patients varied from two to thirty-nine months, with an average of 17.7 months.

Five of the eight patients reported loss of weight. This finding was not commented upon in the records of the other three patients.

An abdominal mass was described in three of the cases. Six patients had draining sinuses, one of which was a draining wound after colpotomy. On pelvic

On cross section, few or numerous, large and small, regular or irregular cavities are seen; these are filled with pus of varying color in a meshed network of milky-white to grayish black connective tissue. This gives the cut surface a cheesy, spongy, moth-eaten, or honeycomb appearance. As a rule, the pus is thick and slimy, and it varies in color and quantity. Granules of varying color and shade sometimes are found in the pus.

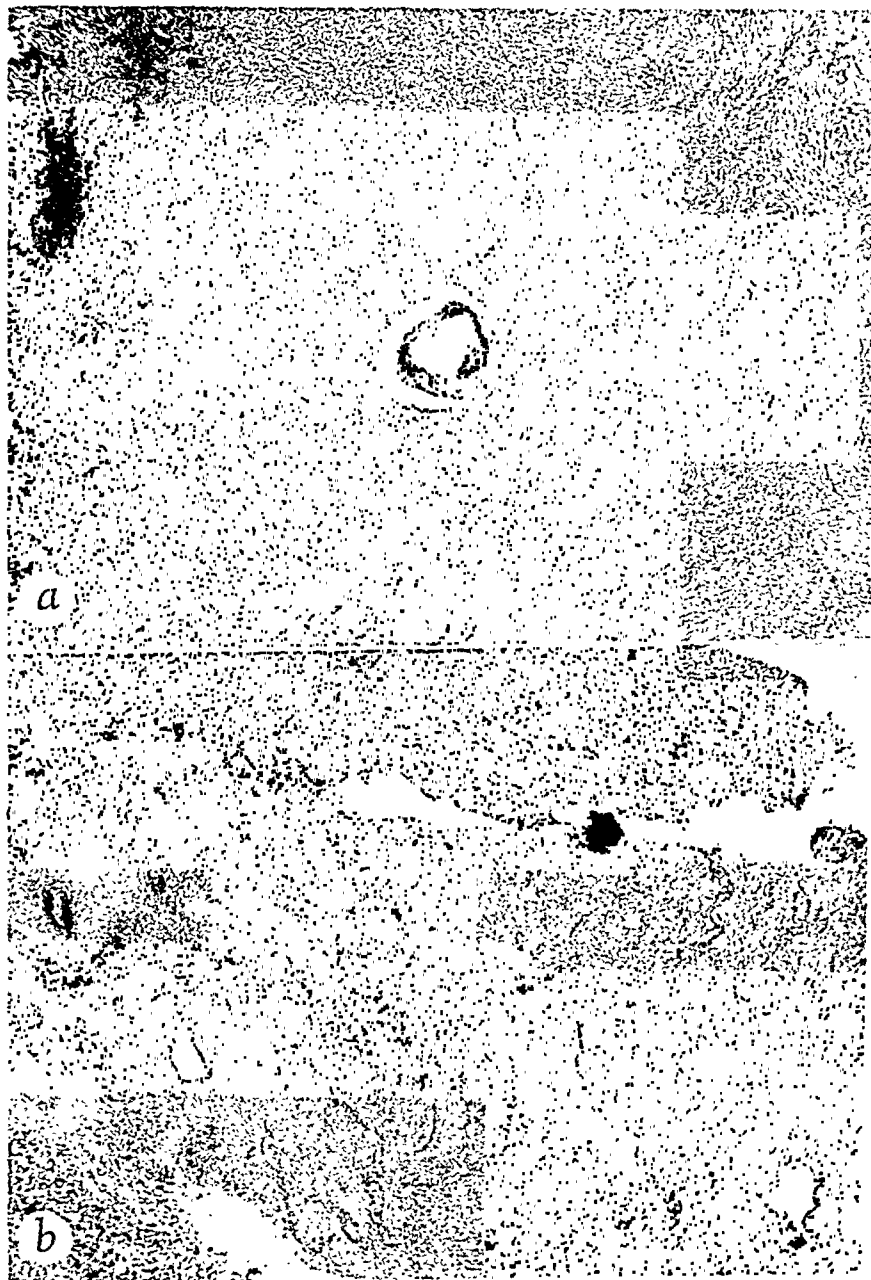


Fig. 2.—*a* (Case 7), Colony of actinomycetes organisms in a small abscess surrounded by granulomatous fibroblastic stroma (hematoxylin and eosin,  $\times 32$ ); *b* (Case 8), A very small colony of actinomycetes organisms (the only colony on this particular slide), showing normal character of the blood vessels in the granulomatous stroma (hematoxylin and eosin,  $\times 32$ ).

In some cases only the ovaries are involved; in others the Fallopian tubes also are invaded. Generally, there are inflammatory changes in the Fallopian tubes, even if no colonies of *Actinomyces* can be demonstrated. Infection of the



by bacteriologic studies after extensive surgical treatment had been carried out elsewhere, were treated intensively with potassium iodide given by mouth, sodium iodide given intravenously, roentgen rays and radium. At the time of this writing, one of these was reported as being "cured" thirty-six months after treatment at the clinic; the other was reported as being "improved" two months after treatment at the clinic. The third patient in this group of three underwent salpingo-oophorectomy on the left and incision of an abscess in the left flank. This patient (Case 3) died on the twentieth postoperative day, from generalized peritonitis. The diagnosis in this case had not been established during the life of the patient.

The other five patients were seen after sulfonamide drugs and penicillin had become available. Four of these five were treated by radical surgical methods. The other patient (Case 6) was seen after extensive surgical treatment had been carried out elsewhere, and the disease had spread to the wall of the chest and the buttocks. She was treated with huge doses of penicillin, with marked regression of the actinomycotic lesions, but she died six weeks after her last visit to the clinic, when the disease became complicated by chronic glomerulonephritis. Of the four patients operated on, three received intensive chemotherapy postoperatively. In the fourth case the abscesses evidently had been sterilized by intensive preoperative therapy with sulfadiazine and penicillin. Two of these patients are reported as being "cured" thirty-three months and ten months, respectively, after treatment at the clinic. The other two were reported to be "improved" one month after operation.

In general, the dose of the sulfonamide drugs, when these were used, was standard for the patient's age and weight. Sulfadiazine was the drug of choice. Penicillin was administered in large doses, the usual course being 2,000,000 units given intravenously or intramuscularly daily for a period of ten days, and repeated as often as necessary to get the desired clinical results.

In summary, three of the eight patients were treated prior to the era of chemotherapy. Of these three, one was reported as "cured," one was "improved," and one died. Of the five patients who received sulfonamide drugs and (or) penicillin, two were reported as "cured," two as "improved" and one died. Three of the eight patients were not operated on; of these, one was reported as "cured," one as "improved," and one died. Of the five who received surgical treatment, two are reported as "cured," two as "improved" and one died. The totals for all eight patients are: three "cured," three "improved" and two dead.

### Comment

It was felt, in respect to our cases as well as to those in the literature, that the chewing of grains and grasses, contact with animals, or contact with patients who had actinomycosis were not etiologic factors. It is generally accepted that the etiologic organism is *Actinomyces bovis*, although in our eight cases the clinician usually was satisfied with the report "sulfur granules found." This situation also was true in respect to the greater majority of cases reported in the literature. The upper Mississippi River valley area was the habitat of the eight patients involved in this series.

It was impossible to determine the mode of infection in any of the eight cases. Because of previous surgical operations, it could not be ascertained in which side the infection had originated, except in Case 8, in which at first only the left Fallopian tube and ovary were involved. From clinical study of our patients, it can be presumed that the infection was bilateral in five, in the left

examination a mass was noted in seven of the eight cases. In the other case pan-hysterectomy had been done elsewhere, and results of the pelvic examinations were recorded as negative.

The laboratory findings in these eight cases were fairly consistent. The average erythrocyte count was 4,420,000 per c.mm. of blood; the average value for hemoglobin was 9.6 Gm. per 100 c.c. of blood. Six of the eight patients had an elevated leucocyte count; the elevation averaged 13,100 cells per c.mm. of blood. A sedimentation rate was calculated in five cases and found to be elevated in all five. The sedimentation rates (Westergren) varied from 30 to 127 mm. in one hour, with an average of 95.5 mm. in one hour. The urine of six of the eight patients contained pus and (or) albumin. In the other two cases results of urinalysis were negative.

The foregoing description of the records and findings shows little that can be called "typical of actinomycosis." In this series of eight cases, bacteriologic studies were made seven times. In five of these cases results of bacteriologic study were positive for *Actinomyces* and in the other two results were negative. These five positive results led to an early correct diagnosis.

*Diagnosis.*—The diagnosis of actinomycosis of the ovaries and Fallopian tubes usually is made on the basis of microscopic study of tissue removed at surgical operation or by culture. The early symptoms of pelvic pain, vomiting, and fever, and the early finding of a mass in the abdomen or pelvis do not ordinarily lead to a diagnosis of actinomycosis, because these signs are more often associated with pelvic inflammatory disease of other causation. The possibility of actinomycosis should be kept in mind when medical treatment fails, especially if the sedimentation rate remains high. The physicians who saw the eight patients in this series were in an unusually favorable position to make the correct diagnosis, since all the patients had undergone some operation before they came to the clinic and pus was available for study in six of the cases. In spite of this surgical treatment, the diagnosis had been established elsewhere in only one case (Case 6).

Five of the eight patients had draining sinuses on entry, and one had a draining colpotomy wound. Results of bacteriologic studies of pus from four of them were positive for *Actinomyces*.

Five of the eight patients underwent radical surgical treatment which made pathologic diagnosis possible. Colonies of *Actinomyces* were found microscopically in the specimens in four of these cases. The negative result occurred in Case 5, in which the patient had received eight months of intensive chemotherapy thirty months before operation. The diagnosis in this case had been established bacteriologically.

The colonies often are difficult to find with the microscope; repeated sections should be made when grossly the lesion is granulomatous and on section reveals multiple abscesses (Fig. 2, *b*). In Case 8 twenty-three sections were made from the abscessed areas at time of operation. Colonies of the organism were not found after careful study of sections. After this organism had been cultured from the pus, more sections were made from the tissue. Finally, two very tiny typical ray fungus colonies were located (Fig. 2, *b*). In Case 3 the diagnosis was not established until after necropsy, when the tissue removed at surgical operation was restudied for the possibility of *Actinomyces*.

In summary, the diagnosis in these eight cases was established either by culture (five times) or by microscopic study of sections of tissue (four times) or by both methods (once).

*Treatment and Results.*—The treatment of these eight patients was medical and surgical. When surgical treatment was employed, it was radical, with removal of all of the diseased tissue possible. Three of the eight patients were seen prior to the era of chemotherapy. Two of these, whose condition was diagnosed

ment. The diagnosis is best made at time of operation, by microscopic examination of fresh tissue and (or) bacteriologic studies of the pus.

From a bacteriologic point of view, the diagnosis is easy when sulfur granules are found in pus from abscesses or sinuses. However, the granules are not always easy to find. They are described as yellow and sagolike to white and sandlike in appearance. They cannot be recognized grossly, and many things can be mistaken for them: "pearls" of degenerated malignant tissue, small concretions or seeds from intestinal fistulas, small round masses of fibrin, masses of cocci, tuberculous debris, and crystals of iodoform. The pus should be strained through gauze and the granules obtained, soaked with strong sodium hydroxide on a glass slide, crushed, and stained by Gram's method. An alternative method is to embed the centrifuged sediment of pus in hard paraffin, make sections, and stain them with hematoxylin and eosin. Examination of the granules under the microscope usually will be conclusive. The disease may be advanced and suppurating many months before a search for the organism is rewarded. The organism may disappear from the pus after secondary infection has begun. Dorling<sup>12</sup> suggested that to obtain material for study, it is better to curet sinuses than to swab them. To add to the difficulty, Rosebury<sup>16</sup> wrote that *Actinomyces israeli* may fail to show clubs, and that similar if not identical clubs may be found in other disease processes, notably actinobacillosis.

*Actinomyces* is difficult to isolate and culture, which not only makes the diagnosis difficult but also gives trouble in testing for the sensitivity of the organism to drugs such as penicillin. Greenblatt and Greenblatt stressed the importance of routine anaerobic as well as aerobic culture techniques and recommended media containing sulfhydryl compounds. In the eight cases in this study, bacteriologic studies were made seven times and results were positive five times.

Pathologic diagnosis also may be difficult. Some sections may readily show numerous colonies of the organisms. Other areas with the same typical picture may show no colonies. This difficulty frequently is commented on in the literature, and it was encountered in the five specimens examined in this study. In two specimens they were found only after careful search of many sections (Fig. 2, b). In the remaining specimen they were not found. It is apparent, in view of these observations, that when actinomycosis is suspected, numerous sections must be made and carefully studied before diagnosis of the disease can be made.

The treatment of pelvic actinomycosis is both surgical and medical. Most authors agree that all diseased tissue should be radically removed whenever possible. Ninety-five per cent of the patients reported on in the literature underwent surgical treatment. In the eight cases reported herein, all the patients had undergone operations before they came to the Mayo Clinic, and five underwent additional surgical procedures at the clinic.

Many forms of medical treatment have been used in actinomycosis, and the favor accorded each has undergone changes through the years. Although the different forms of therapy have been used in combinations, they will be discussed separately.

adnexa in two, and in the right adnexa in one. In none was infection by way of the vagina and cervix suspected. Gardiner and Welsh wrote that the right ovary probably is the prime seat of pelvic actinomycotic infection. However, a summary of one hundred nine cases reported in the literature shows that the infection was bilateral in 44.4 per cent, on the right side in 37.8 per cent, and on the left in 17.8 per cent. Thus, in this respect, our cases differed little from those in the reports of other authors. It has to be assumed that the infection was endogenous and originated from some spot in the gastrointestinal tract.

The five available pathologic specimens in the eight cases exhibited the typical picture described uniformly in the literature. The Fallopian tubes and ovaries were the chief sites of the actual infection, although there were often inflammatory changes in the uterus and parametrium. In all five the pathologic picture was that of multiple granulomatous actinomycotic abscesses, with many dense and loose adhesions to surrounding structures and the frequent formation of sinus tracts.

The typical clinical history, as described in the literature, is that of a previously healthy woman who suddenly becomes ill with localized or diffuse lower abdominal pain, nausea, vomiting, and fever, or one who experiences gradual onset of symptoms referable to the pelvic organs, often with intermittent, more acute exacerbations. The menstrual periods may or may not be disturbed. Only occasionally does the patient detect a tumor mass, but frequently an operation for a pelvic tumor has been performed. In seven of our eight cases pain in the lower part of the abdomen was a prominent symptom. Six of the eight patients had fever, three had been nauseated and had vomited, and only one had noticed any swelling in the abdomen. All eight patients had undergone surgical operation elsewhere.

In the cases in the literature the ages of the patients ranged from fourteen to sixty-four years, with an average of 34.1 years. In the eight cases in the present series the range was twenty-three to forty-six years, with an average of 34.4 years.

The duration of symptoms in the cases in the literature varied from one month to 156 months, with an average of 19.4 months. The duration in the present series was two to thirty-nine months, with an average of 17.7 months.

In the usual case in the literature, loss of weight was reported, abdominal and (or) pelvic masses were described, anemia and leucocytosis were noted, and the sedimentation rate (when reported) was elevated. Of the eight patients reported on in this study, five had lost weight, seven had abdominal and (or) pelvic tumors, seven had hypochromic anemia, six had leucocytosis. Of five sedimentation rates reported in this series, all were elevated.

As can be seen from the foregoing, it is generally impossible to diagnose actinomycosis of the pelvic organs on the basis of the history and clinical findings. Serologic tests, agglutination tests, complement fixation reactions, and skin tests with culture filtrates have been tried, but render little help. The physician must be ever alert to suspect actinomycosis in cases of pelvic inflammatory disease which does not respond to medical or conservative surgical treat-

**Penicillin.**—The latest drug available for the treatment of actinomycosis is penicillin. In the test tube *Actinomyces bovis* reacts poorly to penicillin when compared to the Oxford standard staphylococcus in the ratio of 1:3. However, Jones and Brownell, Walker and Hamilton, Herrell, Nichols, and Heilmann and others reported favorable results from the use of penicillin in clinical actinomycosis. The sensitivity of different strains of *Actinomyces* varies widely, and it is therefore best, in calculation of the proper dose, to test the strain recovered in a given case in glucose broth with varying concentrations of penicillin. Most authors used huge doses of penicillin in practice. In none of the one hundred nine cases of actinomycosis of the ovaries reported in the literature did the patients receive penicillin, but penicillin has been used in actinomycosis of other organs with good results. Four of our eight patients received penicillin; two were reported as cured, one as improved, and one dying of advanced actinomycosis complicated by glomerulonephritis.

In summary of treatment, it might be well to outline Darling's plan of therapy for abdominal actinomycosis:

Prophylaxis. Early appendectomy when appendicitis is diagnosed.

Surgery. The ideal is radical excision of diseased tissue.

Local oxygenation with hydrogen peroxide, Carrel-Dakin fluid, or zinc peroxide in suspension.

Iodides. Preferably potassium iodide in doses of 5 grains (0.3 Gm.) administered three times daily, the dose being gradually increased to 200 grains (13 Gm.) daily.

Sulfonamide drugs. Three repeated courses, with an interval of a week between courses.

Penicillin. Local instillation and parenteral injection.

Roentgen therapy.

General measures, such as rest and use of tonics and vitamins.

Of the 109 cases in the literature, 102 are accompanied by reports of results. In these 102 cases twenty-five patients, or 24.5 per cent, presumably were cured; fifteen, or 14.7 per cent, were improved, and sixty-two, or 60.8 per cent died. In the eight cases reported in this study, three patients, or 37.5 per cent, presumably were cured; three, or 37.5 per cent, were improved, and two, or 25 per cent, died. Although the present series was too small to permit the formation of conclusions as to efficacy of treatment, the results of treatment compared favorably with those reported in the literature.

## Conclusions

Actinomycosis of the ovaries and Fallopian tubes is one of the less common, yet serious, diseases of the female pelvic viscera. It is a disease with which every gynecologist and abdominal surgeon should be familiar. The causative organism usually is *Actinomyces bovis*. The organism is a normal inhabitant of the alimentary tract, which usually is the origin of the infection, although entry by way of the vagina is possible. The habit of chewing grain or grasses and contact with animals or human beings afflicted with actinomycosis are not etiologic factors in the disease. The Fallopian tubes and ovaries are the usual sites of the infection. The gross pathologic picture is one of a spongy, honeycombed, granulomatous mass with adhesions and sometimes with sinuses to surrounding structures. The microscopic picture is that of multiple abscesses encased in a granulomatous fibroblastic stroma. The fungi are typically found in the abscesses and in the lining of the accompanying sinus tracts. Actinomycosis spreads by direct extension or by the blood stream. It rarely spreads by way of lymphatic vessels. The clinical picture of the disease

*Iodides.*—According to Wright, Nocard in 1892 was the first to utilize potassium iodide in the treatment of actinomycosis in man. Since that time it has been used constantly. The theory of the action of iodides is that when they are absorbed, they combine with proteins, liberating free iodide, which has the action of a counterirritant and may tip the balance in favor of the tissues by vascularizing the part and increasing leucocytic action. This may cause early softening of the tissue and extrusion of the organism. Iodine may neutralize the action of agents which prevent solution and absorption of necrotic tissue, thus laying bare the organism to real germicidal agents. In vitro, the growth of *Actinomyces* is not retarded by concentrations of potassium iodide up to 2 per cent. Thus, there is no scientific proof that potassium iodide is of value. However, it has been and still is used in gradually increasing doses up to 100 grains (6.5 Gm.) administered three times a day. A 10 per cent solution of sodium iodide has been used intravenously, 30 to 40 c.c. being administered the first day and the dose being gradually increased until 100 c.c. per day are being given. Iodides were used in three of the eight cases reported in this study.

*Iatron.*—This drug has been used occasionally. It is believed to mobilize the defense mechanism of the body rather than to exert any specific action on *Actinomyces*. It is given intravenously. It is a dangerous drug, since it may induce functional disturbances of the liver. It was not used in our eight cases.

*Gold Vaccine.*—Déak in 1941 reported that in twenty-two months, he had cured a patient of genital actinomycosis by means of gold vaccine. The patient also received roentgen therapy, but this was stated to be of no help. Gold vaccine has rarely been used.

*Actinomyces Vaccine.*—It was said<sup>37</sup> that Colebrook about 1920 attempted to carry out active immunization of the patient by the use of vaccine therapy. He came to the conclusion that it was of no value without surgical treatment also, but he noted improvement in patients for whom drainage of abscesses was carried out. Macnab used stock polyvalent vaccine in doses of 1 to 4 c.c. (1 c.c. containing 2,500,000 fragments of the mycelium) by injection on alternate days for a period of three weeks. Vaccines were not used in our eight cases.

*Roentgen Therapy.*—According to Gardiner and Welsh, Harsha in 1904 first used roentgen therapy on actinomycosis with success. Since 1904 roentgen rays have been used in varying doses and courses. Radium has also been used. Although roentgen rays in the form of ten erythema doses do not kill *Actinomyces* in pure culture, they do favorably affect the disease, probably because of the reaction of the tissue. Desjardins concluded that roentgen rays are powerful therapeutic agents against *Actinomyces*. McWhirter reported excellent results obtained with roentgen therapy in all types of the disease. This form of treatment was used in three of the eight cases in this study.

*Thymol.*—After studying twenty-two different volatile oils, Myers and Thienes<sup>32</sup> in 1925 and Myers<sup>30, 31</sup> in 1927 and 1937 advocated the use of thymol in actinomycosis. Joyce recommended a dose of 1.5 Gm. of thymol administered in capsules two days out of every three until 60 Gm. have been given, and this was to be accompanied by daily irrigation of sinus tracts with a 10 per cent solution of thymol in olive oil. Bancroft and Stanley-Brown used slightly larger doses. Thymol was not used in the eight cases reported in this study.

*Sulfonamide Therapy.*—Sulfonamide drugs were used for actinomycosis shortly after they had been discovered. Walker<sup>44</sup> in 1938 was the first to report favorable results from the use of sulfanilamide in abdominal actinomycosis. Other reports soon followed.<sup>14</sup> Benbow, Smith, and Grimson used various sulfonamide drugs, but preferred sulfadiazine. Lyons, Owen, and Ayers secured striking results with sulfonamide drugs in all clinical types of actinomycosis. Cutting and co-workers<sup>7, 11, 12</sup> found sulfathiazole and sulfadiazine to be most effective in vitro, and recommended that the concentration of the drugs in the blood be kept higher than 9 mg. per 100 c.c. In the literature there are only five reports of cases in which sulfonamide drugs were used in actinomycosis of the tubes and ovaries. Of the patients concerned, four died and the condition of one was improved. However, in the literature from 1941 to 1946 only nine cases were reported in which sulfonamide drugs were used for this disease, so that conclusions cannot be drawn on the basis of so small a series. In the eight cases reported in this study, sulfonamide drugs were used in three, with one patient being reported as cured and two as being improved.

### Method

For the purpose of population screening it was necessary to devise a method for obtaining vaginal discharge quickly, easily, and at low unit cost. The techniques previously described were too complicated. A damp cotton swab applicator protected by a sheath was devised. The sheath was of cardboard or rubber tubing, one-fourth inch in diameter and five inches in length with one end beveled. A standard applicator stick was used (Fig. 1).

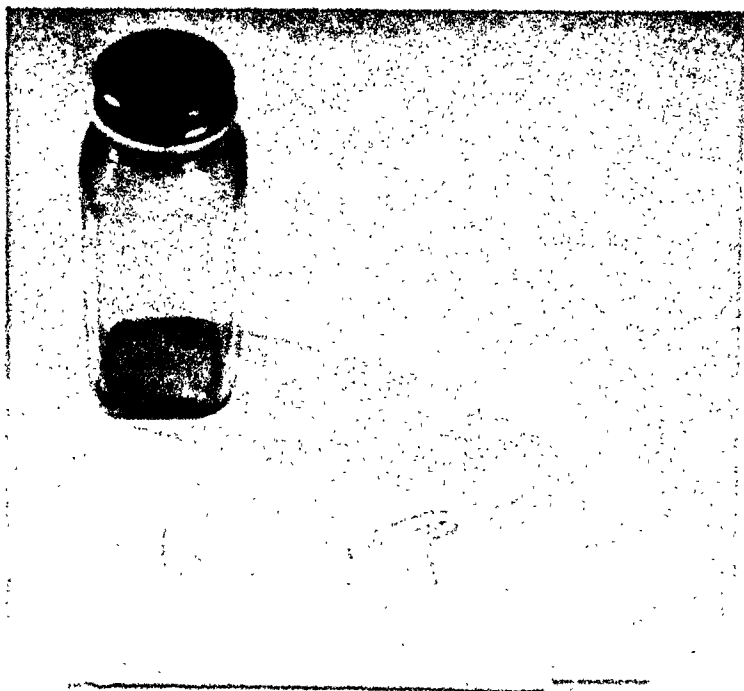


Fig. 1.—Equipment necessary to obtain a vaginal smear by the sheath method.

The sheath containing the applicator is inserted along the posterior vaginal wall to the cul-de-sac. The swab is then pushed beyond the sheath and a sample of the discharge obtained by a circular motion. The swab is then withdrawn into the sheath and the entire unit removed. The applicator is again pushed forward and the discharge rapidly smeared and tapped on a labeled, clean glass slide. Before the smear has time to dry, a matter of a few seconds, it is dropped into a small bottle containing equal parts of 95 per cent alcohol and ether. (A paper clip previously slipped over one end of the slide keeps it from adhering to other slides in the bottle.) The bottle is then stoppered securely, and the sheath and applicator discarded. By this method as many as 250 smears were taken by one individual in a single day.

In the laboratory the slides were stained by the Papanicolaou technique. They were scanned by trained technicians, and all smears presenting unusual cells were interpreted by the authors. Smears were designated as "negative," "suspicious," or "positive" for the presence of cells believed to have originated from carcinoma.

Smears were classified as negative when only normal cell types were seen, and leucocytes and erythrocytes were not prevalent. Smears were classified as positive when they contained clumps of abnormal cells, leucocytes in abundance, old or hemolyzed erythrocytes, and a "dirty" background of cellular debris and

## THE VAGINAL SMEAR IN POPULATION SCREENING FOR UTERINE CARCINOMA\*

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INTEREST in cytology was stimulated in 1917 by Stockard and Papanicolaou,<sup>1</sup> who used vaginal smears in a study of the estrous cycle in guinea pigs. During the next few years, their use was largely limited to studies of physiologic cellular changes during the human menstrual cycle and in pregnancy.<sup>4, 5</sup> In 1931, MacCarty presented the first of three<sup>2, 3, 6</sup> reports dealing with the characteristics of immature cells, especially with regard to the nucleo-nucleolar ratio.

Vaginal smears were first evaluated in the detection of uterine carcinoma by Papanicolaou,<sup>7, 8</sup> who described the staining procedure which bears his name and which has facilitated interpretation of the cytologic picture. The appearance in 1943 of a monograph by Papanicolaou and Traut<sup>9</sup> initiated the present wide interest in the cytologic detection of genital carcinoma. Subsequently, many articles and a handbook on vaginal cytology have appeared.<sup>10-26</sup>

Whether the use of vaginal cytology is more valuable as a screening procedure or as a diagnostic method is controversial.

Papanicolaou stated: "It [the vaginal smear] is not recommended as a means of ultimate diagnosis. It should be used as a preliminary or sorting procedure and should be confirmed as a matter of routine by biopsy and tissue diagnosis."<sup>9</sup> Fremont-Smith, Graham and Meigs have said: "It is not our purpose that this new test should compete with the biopsy or replace that method in the diagnosis of cancer."<sup>27</sup> Gates and Warren declared: "Overemphasis on the statistical accuracy seems to put the stress in the wrong place. If the method is to be used as a preliminary or sorting procedure, the degree of accuracy is unimportant within reasonable limits. The thing that matters primarily is whether the method will discover cancer and initiate treatment earlier than would otherwise be done."<sup>18</sup>

It was decided to evaluate the vaginal smear as a population screening method for selecting a group of women in whom subsequent clinical and histologic examinations would reveal a high incidence of malignancy.

### Material

Vaginal smears were obtained from 5,314 women representing three different segments of the population. The first group included 2,594 women, mostly over 30 years of age, admitted to the University Hospitals between April 1, 1947, and April 1, 1948. The second consisted of 1,482 inmates of two State mental institutions who were predominantly postmenopausal. The third was made up of 1,238 women over 30 years of age from Washington County, Iowa, who volunteered for the examination.

\*This project has been supported by grants from the Iowa Division of the American Cancer Society.



no histologic verification. No malignancies were found in three women with positive smears even after thorough clinical and histologic examinations. The significance of the remaining three positives is unknown since the patients could not be followed clinically and no biopsies were taken.

## CANCER SURVEY

CONSECUTIVE ADMISSIONS (OVER 30 YRS)

2594

EVALUATION BY

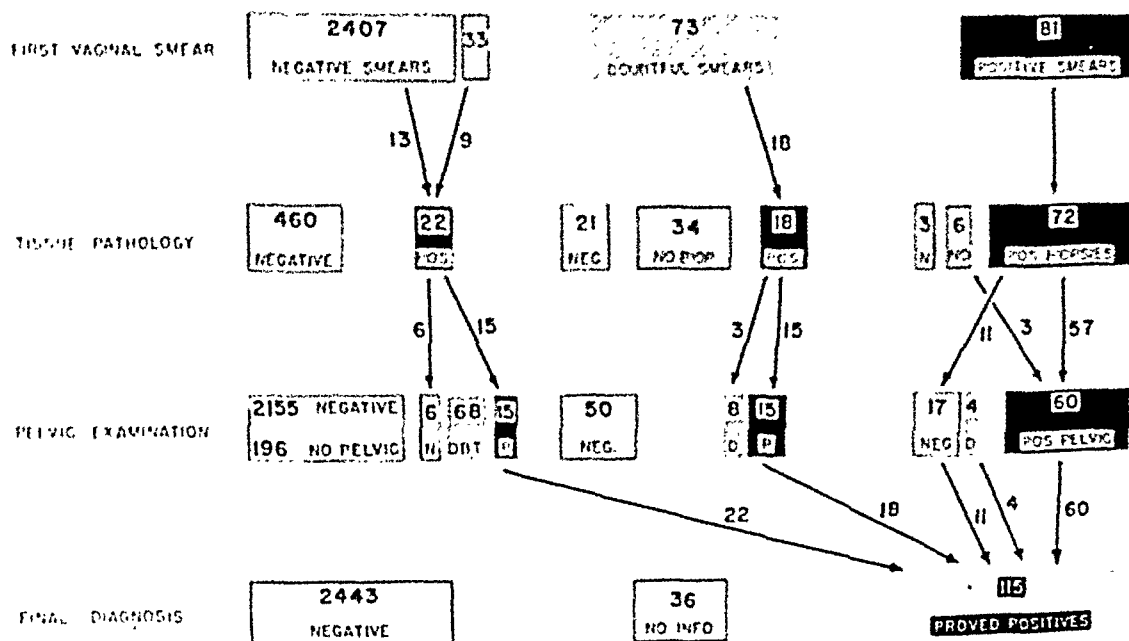


Fig. 2.—Comparison of three methods, cytologic, histologic, and clinical, in the detection of pelvic carcinoma in women admitted to the University Hospitals from April 1, 1947, to April 1, 1948.

Pelvic examinations were done on 2,398 of the 2,594 women in the hospital series. Among the 81 patients with initial positive smears, 60 had gross malignant lesions, 4 were clinically suspicious, and 17 were negative. Further clinical and histologic studies on these 17 patients revealed eleven cervical carcinomas; seven were interpreted as carcinomas in situ and four as early invasive carcinomas.

Histologic examinations were made on 636 patients (Fig. 2). Biopsies or curettings obtained from 72 of those with positive smears revealed carcinoma. No evidence of malignancy was found in 460 cases. In twelve instances the tissues submitted were inadequate for diagnosis, but subsequent biopsies from two of these patients revealed carcinoma. The initial biopsies from two patients were suspicious for malignancy; tissue obtained later showed carcinoma. In seven instances where the first biopsy was negative, subsequent tissue examination revealed a malignancy. The first biopsy from four patients showed carcinoma, but additional histologic studies before treatment could not substantiate the initial diagnosis.

mucus. Smears were designated as suspicious when they contained too few of the positive characteristics and yet gave the impression that they were not normal. They contained such elements as occasional aberrant cells, normal-appearing glandular cells (either in the mid-interval of a menstrual cycle or post-menopausally), large numbers of histiocytes, leucocytes and hemolyzed blood. A smear was judged inadequate when too few cells were present for interpretation or when the preparation was faulty.

Every attempt was made to obtain both clinical and histologic evaluations on as many patients as possible. The University Hospitals patients were usually available for further study. Most of the women with suspicious or positive smears had thorough pelvic examinations, and biopsies were obtained in 51 per cent of the suspicious and in 95 per cent of the positive cases.

The women in the mental institutions who presented abnormal cytologic pictures were subjected to pelvic examinations and additional smears. Biopsies were obtained from 42 per cent of this selected group.

The majority of the original and repeat smears from the women of Washington County were obtained in physicians' offices. Where no physician was available, smears were taken by a trained nurse. Pelvic examinations were done and biopsies obtained either by home physicians or at the University Hospitals.

## I. Proof of Method

### *Analysis of University Hospital Series.*—

Fig. 2 presents the results obtained from the cytologic, histologic, and clinical evaluation of 2,594 women in the University Hospital series. This survey served as the basis for the evaluation of vaginal smears since the findings could be compared with those of the clinical and histologic methods commonly employed to diagnose genital malignancy.

Of the 2,594 first vaginal smears, 2,407 were interpreted as negative, 33 inadequate for interpretation, 73 suspicious, and 81 positive.

From the cytologically negative group, thirteen were later proved to have genital cancers. Eight were considered clinically positive and five clinically negative. Seven of the thirteen with false negative smears had adenocarcinomas of the uterine body as proved by curettage, and six had epidermoid carcinoma of the cervix revealed by biopsy. Second smears from eleven of these thirteen patients revealed abnormal cells. One patient had seven negative smears before abnormal cells were found, and the other had twelve negative smears. In this last case, an epidermoid carcinoma of the cervix, abnormal cells were found only after vigorously scraping the surface of the lesion.

Among thirty-three women with unsatisfactory first vaginal smears, nine were found to have genital malignancies. During the initial pelvic examination seven of the nine revealed obvious cancers; one was considered suspicious, and the other negative. Three of the group had adenocarcinomas of the body (one an adenoma malignum), and six had epidermoid carcinomas of the cervix. Adequate additional smears were obtained from four of these nine cases and three were interpreted as positive. The patient with adenoma malignum had four negative smears. No additional smears were obtained from the remaining women.

Smears from 73 patients were interpreted as suspicious. Histologic data were obtained on 39 of these women; 18 were shown to have cancer, and 21 were negative. A benign gynecologic lesion was found in each of the 21 patients after adequate clinical and histologic studies. This group included six instances of endometrial hyperplasia, five of endocervical or endometrial polyps, and ten of acute or severe chronic cervicitis. No biopsies or clinical follow-ups could be obtained on the remaining 34 patients.

Among 81 patients with positive smears, 75 were proved to have genital malignancy including three with advanced carcinomas on whom there was

## II. The Use of the Vaginal Smear as a Screening Procedure

The University Hospital series of 2,594 women served to evaluate the vaginal smear method because findings could be correlated with clinical and histologic studies. However, if this series is reconsidered on the basis of a screening procedure the results can be listed in the same manner as those for the institutional and Washington County surveys.

From the total of 2,594 vaginal smears, 154 were suspicious or positive (Table II). The smear findings would have indicated the need for thorough clinical and histologic study of this group. When these latter studies were done, 93 cases of genital malignancies were found. In eleven instances, pelvic examinations failed to detect the presence of cancer, but tissue from seven revealed carcinoma in situ and four showed early invasive carcinoma of the cervix.

TABLE II. EVALUATION OF 2,594 VAGINAL SMEARS FROM CONSECUTIVE FEMALE ADMISSIONS TO THE UNIVERSITY HOSPITAL

2,594	Patients studied by single vaginal smear
33	Unsatisfactory smears
154	Suspicious or positive smears
2,398	Pelvic examinations
636	Biopsies
93*	Carcinomas found

\*There was a total of 115 genital cancers—13 were missed by the initial adequate smear and in 9 the initial smear was inadequate for interpretation.

The survey of the inmates of two mental institutions was based on smears from 1,482 women (Table III). The slides from 43 patients were unsatisfactory and additional smears were obtained. Twenty-seven smears were suspicious or positive. Subsequent pelvic and histologic examinations on this group of 27 showed five previously undetected genital cancers, one of which was carcinoma in situ.

TABLE III. EVALUATION OF VAGINAL SMEARS FROM 1,482 INMATES OF TWO STATE MENTAL INSTITUTIONS

1,482	Patients studied by vaginal smear
43	Unsatisfactory or menstrual smears
27	Positive or suspicious smears
67*	Pelvic examinations
28	Biopsies
5	Carcinomas found

\*This disproportionate number of pelvic examinations was done because of interest aroused by Ayre's speculation that high cornification counts on cervical smears are due to a concentration of estrogen in infected cervical tissues. He believes a local concentration of estrogen is a growth stimulating factor predisposing to cancer.<sup>25, 26</sup> Seventeen women over 62 years of age showed excessive numbers of cornified cells. Pelvic examinations were done on all of these patients and cervical biopsies obtained from three. No genital malignancy was found.

Smears were taken from 1,238 Washington County women; 1,228 were negative, six were suspicious, and four positive for abnormal cells (Table IV).

TABLE IV. EVALUATION OF VAGINAL SMEARS FROM 1,238 WOMEN RESIDING IN WASHINGTON COUNTY, IOWA

1,238	Smears obtained
10	Positive, 4; suspicious smears, 6
14	Resmears or pelvic examinations requested
6	Biopsies
3	Carcinomas found

In the four patients with positive smears, unsuspected malignancy was proved histologically in two. The third patient (E. P.) with two positive smears was subjected to

In the final evaluation based on cytologic, histologic, and clinical findings, 2,443 patients were negative, 115 had proved genital cancer, and the remaining 36 were incompletely followed.

Three patients were admitted to the University Hospitals with diagnoses of genital carcinoma based on histologic studies made elsewhere. Repeated vaginal smears were negative and no histologic evidence of malignancy was found in tissue removed in this hospital. These three cases were not included in the survey.

Eight patients had ovarian malignancies; two of these women showed abnormal cells in the vaginal smear. In these two instances, laparotomy established the diagnosis of adenocarcinoma of the ovary with no evidence of uterine involvement. Apparently the abnormal cells had migrated down the Fallopian tubes to the uterine cavity and hence into the vagina.

Table I presents the histologic types of the malignancies encountered as well as the number of each in the hospital series.

TABLE I. HISTOLOGIC CLASSIFICATION OF 115 PELVIC CARCINOMAS FOUND IN 2,594 CONSECUTIVE ADULT FEMALE ADMISSIONS TO THE UNIVERSITY HOSPITALS

NUMBER OF CASES	TYPE
64	Epidermoid carcinoma of the cervix
7	Carcinoma in situ of the cervix
4	Adenocarcinoma of the cervix
30	Adenocarcinoma of the corpus uteri
3	Epidermoid carcinoma of the vulva
2	Epidermoid carcinoma of the vagina
2	Adenocarcinoma of the ovary
1	Adenocarcinoma with pelvic metastases, primary site unknown
1	Transitional cell carcinoma of the bladder involving the vaginal wall
1	Adenocarcinoma of rectum involving the vaginal wall

### *Summary of Results of Hospital Series.—*

In the University Hospital series, the initial positive or suspicious vaginal smears corresponded with the clinical and histologic findings 93 times in 115 proved genital malignancies. In 13 patients the first smear did not detect the malignancy, and in nine the initial smear was inadequate. From 16 of these 22 patients a second smear was obtained; 14 showed abnormal cells. Genital malignancy has not yet been proved in three women presenting positive smears. However, in each instance where the smear was interpreted as suspicious or positive and adequate clinical follow-up was made, some gynecologic disorder was found.

The initial pelvic examination correlated with the final diagnosis of malignancy in 98 of 115 cases in the University Hospital series. In seventeen instances, the initial pelvic examinations failed to reveal malignancy, but, in eleven, positive cytologic findings led to further investigations which revealed the presence of carcinoma. In the remaining six patients, the malignancies were found in biopsies taken during the routine management of what had been considered benign lesions.

The initial cervical biopsy or curettings revealed carcinoma in 101 of the 115 cases of malignancy. No tissue was obtained from three patients with far-advanced carcinoma. In eleven patients the first biopsies failed to reveal the carcinoma (seven negative, two inadequate, and two suspicious); but, because of suspicious clinical or cytologic findings, subsequent biopsies were done and demonstrated malignancy.

or positive smears. The liberal use of the suspicious category was believed justified by the fact that even when no malignancy was present, there was invariably some benign genital lesion present. Treatment of these lesions is not necessarily prophylactic against cancer, but it is certainly wise to eliminate any condition which might predispose to malignancy.

Certain medical and lay publications have given an erroneous impression of the diagnostic value of vaginal smears. Obtaining and preparing a sample of vaginal discharge are rapid and simple procedures but interpretation of the smears is difficult. This should not be attempted without many months of intensive study of smears from women of all ages and with a wide variety of genital lesions. The vaginal smear technique is a valuable adjunct in the fight against cancer, but it is useful only so long as it is properly evaluated and correctly used.

These data place the detection of genital cancer in a new perspective with the cytologic added to clinical and histologic examinations. In the 115 genital cancers in the hospital series, the initial cytologic examination missed 13, the initial histologic examination seven, and the initial clinical evaluation 17. Each of the three methods alone shows a significant error rate, but, by combining all three, there is an improved chance of detecting any existing genital malignancy.

TABLE V. FREQUENCY OF DETECTION OF CARCINOMA AT THE INITIAL OBSERVATION BY THREE DIFFERENT METHODS

	NO.	PER CENT
Total number of proved malignancies	115	100
Number found positive on:		
First vaginal smear	102	88
First biopsy	108	94
First pelvic examination	98	85

Summary

A technique was devised to obtain a sample of the vaginal discharge easily, quickly, and at low unit cost. Vaginal smears were taken on 5,314 women representing three population segments: general hospital admissions, institutional inmates, and the female population of an Iowa county.

The established clinical and histologic methods of diagnosing genital malignancy were used to determine the efficiency of the vaginal smear as a population screening procedure. The cytologic examination has proved to be of value when used in this manner.

Conclusions

1. Screening of the female population for uterine carcinoma by use of the vaginal smear technique is feasible and valuable provided adequately trained personnel is available.
2. A simplified technique of obtaining a sample of vaginal discharge was devised to adapt the vaginal smear method to population screening.
3. The cytologic method can be used to select those women who need further evaluation by clinical and histologic studies.
4. Each of the methods (cytologic, clinical, and histologic) alone shows an appreciable error rate.
5. It is believed that by coordinating cytologic, clinical, and histologic methods of detection, few genital malignancies will escape detection.

thorough clinical examination and three biopsies were obtained. One of the tissue specimens contained a small area of anaplastic squamous epithelium which was insufficient to make a definite diagnosis. This patient is to return in three months. Clinical examinations and cervical biopsies revealed no malignancy in the fourth patient who presented a positive smear. However, several subsequent smears still showed abnormal cells. She is to return for re-examination in three months.

Smears from six patients were suspicious; additional smears were obtained from five and one could not be followed. One of the repeat smears was positive, one was inadequate, two were negative, and one was retained in the suspicious category because the patient could not be followed. No tissue has been obtained to date from the woman with the positive repeat smear. The patient with the inadequate smear was clinically positive for malignancy, but no tissue could be obtained for histologic examination.

Thus, from a total of 1,238 women, the vaginal smear segregated ten patients for further study and, from these, three were found to have genital carcinoma.

In summary, the use of the vaginal smear as a screening method in these surveys selected 191 women out of 5,314. Subsequent clinical and histologic examinations led to the diagnosis of cancer in 100 of these cases, and in each of the remaining on whom adequate follow-up was made some gynecologic lesion was found.

### Discussion

There are several methods of obtaining cells from the vagina and cervix. The original method introduced by Papanicolaou utilizes a curved glass tube with a suction bulb, and the discharge in the vaginal pool is aspirated and blown onto a slide. Smears made in this manner are usually thicker than those made with the applicator and sheath. The cost of the tubes and bulbs plus the breakage and time consumed in sterilizing each unit makes this technique impracticable for population screening.

Another method, introduced by Ayre,<sup>23, 24</sup> consists of scraping the cervix with a special wooden or metal spatula and spreading the material on a slide. This technique requires the services of a physician, the patient in the lithotomy position, and a speculum in place. This is probably the most accurate technique because visual examination of the cervix can be made and a biopsy can be obtained readily from any suspicious area. For the type of survey presented in this report, it was impossible to obtain adequate personnel, space, and equipment necessary to use this technique.

The sheath method proved satisfactory for population screening and detected a majority of the malignant lesions. The procedure is so simple that an intelligent individual can learn it in a few minutes. The rapidity is illustrated by the fact that one nurse obtained smears from the 1,482 patients in the mental hospitals at the rate of 200 daily. It is recognized that the recent use of either a cleansing douche or a lubricating jelly causes the same difficulties of interpretation here as in the other methods.

The results have been reported in total numbers rather than percentages, since the latter can be computed in many ways to stress different values. Knowing the number of cases in each category, interpretations can be made as desired. It must be stressed that a fair evaluation can be made only by comparing the initial smear with the first biopsy and first pelvic examination.

Multiple vaginal smears on the same patient increase the accuracy of this technique in the detection of genital malignancies. This survey was not designed to determine the efficiency of the vaginal smear but rather to evaluate its use in screening the general female population. Its value in this connection is indicated by the high incidence of genital cancer found in the women with suspicious

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## Appendix

All patients treated for genital carcinoma at the University Hospitals are urged to return for examination in three months and every six months thereafter. During the past 18 months a single smear was taken from such patients at each visit. Two hundred forty-four smears were obtained from 197 patients (Table VI), the majority of whom had been treated with x-ray and/or radium. Smear interpretations were compared with the clinical findings, since only 45 patients were subjected to biopsy.

In 47 patients, pelvic examinations showed clinical evidence of residual malignancy or recurrence. The vaginal smears were positive in seventeen, suspicious in seven, and negative in twenty-three. Recurrence was suspected clinically in twenty-seven; this group showed three positive, one suspicious, and twenty-three negative smears. In the remaining 170 with no clinical evidence of malignancy, there were four positive, 19 suspicious, and 147 negative smears.

TABLE VI. CLINICAL AND CYTOLOGIC EVALUATIONS OF 244 SMEARS TAKEN FROM 197 PATIENTS WITH PREVIOUSLY TREATED UTERINE CARCINOMA

PELVIC EXAMINATIONS	VAGINAL SMEAR FINDINGS		
	POS.	SUSP.	NEG.
47 Positive	17	7	23
27 Suspicious	3	1	23
170 Negative	4	19	147

A negative smear is obviously of little significance. However, the presence of abnormal cells correlated very well with the finding of residual carcinoma in the genital tract. In several instances, the recurrence of pelvic malignancy was detected by smears months before it was evident on examination. It is obvious that recurrent genital cancer which is not on a free surface, i.e., deep pelvic tissue extensions, or distant metastases, does not shed cells that can be detected by vaginal smears. It is also possible that the surface of a residual carcinoma may be sealed off by previous radiation. It seems highly probable that vaginal smears will be less satisfactory in evaluating treated carcinomas than in the initial detection of malignancies.

## Acknowledgments

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Seven hundred fifty-four cases, or 78.8 per cent, developed their symptoms subsequent to the menopause, which would indicate that carcinoma of the fundus uteri is predominantly a postmenopausal disease. The natural menopausal age distribution of these cases reached a peak at the age of 50. The average age of menopause, however, is 49.05 years. This is a somewhat later age than that shown by patients with cancer of the cervix and cancer of the vulva, which are 46.3 and 47.1 years, respectively. Also, this is a later average age for the menopause than reported by Fluhmann<sup>4</sup> for a large sample of normal women. The observation of a delayed menopause in this disease has also been reported by Corseaden and Gusberg<sup>5</sup> who reported the peak in his cases at 52 to 54 years and also by Randall<sup>6</sup> who stated that 35 per cent of his fundus cases menstruated after 50 years of age compared with only 8 per cent noneancerous 15 years following the menopause.

*Marital Status.*—As shown in Table II, there were 105, or 11 per cent, unmarried women among the cases studied. When comparing the various percentages in the different age brackets with the U. S. Census for New York State Rural and Urban population for 1940, there was found to be no significant deviation from that of a standard population. In other words, the ratio of single women to married women is the same as found in a normal population. This figure compares with 11.5 per cent unmarried women as reported by Taylor and Becker,<sup>7</sup> 18.7 per cent as reported by Randall<sup>6</sup> and 24.8 per cent as reported by Corseaden and Gusberg.<sup>5</sup> All of these reports are from clinics in New York State and why there should be such a wide variation in the relative number of unmarried women is not evident. In contrast with these observations on corpus cases, the ratio of single to married women in our cervix cases is definitely less, only 3.8 per cent for the cervix cases and 11.5 per cent for the fundus cases.

A further comparison was made by dividing the married group into two divisions on the basis of term pregnancies, that is, married with no pregnancies and married with no full-term pregnancies. As shown in the lower part of Table II the percentage of women with corpus cancer who comprise this group is significantly greater than the group with cervix cancer. It can be noted from this table that 18.8 per cent of the married women were never pregnant. This figure may be compared with 28.2 per cent as reported by Randall,<sup>6</sup> 31.5 per cent as reported by Taylor and Becker,<sup>7</sup> and 38.6 per cent as reported by Corseaden and Gusberg.<sup>5</sup>

TABLE II. MARITAL STATUS

CORPUS			CERVIX	
	NUMBER	PER CENT OF TOTAL	NUMBER	PER CENT OF TOTAL
Total	957		500	
Unmarried	105	11.0	19	3.8
	NUMBER	PER CENT OF MARRIED	NUMBER	PER CENT OF MARRIED
Total married	842		481	
No term pregnancies	44	5.2	22	4.57
No pregnancies	159	18.9	56	11.62
	203	24.1 ± 1.47%	78	16.2 ± 1.67%

*Weight.*—The weight, height, and age of 772 of the 957 patients were available for a comparison with normal weights. The normal for the different height and weight combinations was obtained from Wood.<sup>8</sup> Table III shows that, using the values of Wood as a “norm,” 75 per cent of the fundus cases are overweight. For comparative purposes, the deviations from the “norm”

## A STATISTICAL STUDY OF CANCER OF THE CORPUS UTERI

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FROM the inception of this institution as a cancer treatment center in 1913, there have been 957 histologically proved cases of cancer of the corpus uteri admitted to the Roswell Park Memorial Institute up to 1943. These cases were reported in part by Schreiner<sup>1, 2</sup> and by Murphy<sup>3</sup> and represent 21 per cent of the total gynecological admissions, while, during the same thirty-year period, cancer of the cervix represented 65 per cent, carcinoma of the vulva, 3.0, carcinoma of the ovaries 9.0, and malignancies of the tubes and vagina 1.1 per cent of all malignancies of the female genitals. It can be observed from these figures that the ratio of fundus to cervix cancer is slightly over 1:3. This is in agreement with other reports of large numbers of cases in the literature.

*Age.*—The age distribution of these 957 cases at the time of admission is shown in Table I. A definite peak is noted at the age period 55 to 59 years. The youngest patient was 10 years of age and the oldest 86. The rate of incidence was computed using the female population of New York State, 1940 census, as a standard. These data are also included in Table I and show that the highest incidence is in the age bracket 65 to 69 years. The rates as shown for the various age brackets are not to be considered the actual incidence of fundus carcinoma in the State of New York, since this sample of 957 cases represents only a small portion of all cases of this type in this state.

TABLE I

AGE AT ADMISSION	NUMBER	RATE PER 10,000
10-19	2	
20-24	9	.1517
25-29	4	.065
30-34	14	.236
35-39	26	.462
40-44	42	.791
45-49	84	1.76
50-54	138	3.38
55-59	198	6.21
60-64	184	6.95
65-69	151	7.28
70-74	71	4.95
75-79	29 }	2.32
80-	5 }	
Total	957	

*Menarche and Menopause.*—The distribution of the incidence of menarche reached its highest level at the age of 13 years. The earliest occurred at the age of 8 and the latest at age 22, an apparently normal incidence and distribution.

and our incidence is so nearly that of Master's, we conclude that there is no significant difference in the incidence of hypertension between the corpus cancer cases and their corresponding age-sex group in the general population.

*Symptoms.*—The most common symptom found in the cases of carcinoma of the fundus uteri was bleeding which occurred in 80.5 per cent of the cases. This symptom is divided into postmenopausal bleeding 63 per cent and intermenstrual bleeding 17 per cent. The second most common symptom was discharge without frank blood which occurred in 15.9 per cent of the cases and pain and pressure symptoms in 4.2 per cent. Comparing the various symptoms, Taylor and Becker<sup>2</sup> found that bleeding as the primary symptom occurred in 96.6 per cent of his cases.

*Pathological Classification.*—The pathology of the 957 cases of fundus cancer was found to be as follows:

Adenocarcinoma fundus uteri	917 cases
Leiomyosarcoma	31 cases
Squamous cell carcinoma	7 cases
Endometrial sarcoma	3 cases
Deciduaoma	2 cases

During this same period there were 121 cases of adenocarcinoma which were classified here as cervix cases, rather than corpus cases. This is contrary to the usual classification as primary corpus cases. Of the 917 cases of adenocarcinoma of the fundus, 786 cases were graded pathologically and are shown in Table IV. The distribution of the pathological grades shows the largest percentage in Grade I and a progressively lower percentage in the following grades. This finding agrees with that of Taylor and Becker<sup>2</sup> who show 63 per cent in their combined grades I and II and 37 per cent in their combined Grades III and IV. For comparative purposes the pathologic grading of 1,134 cases of carcinoma of the uterine cervix are included in Column 2 of Table IV. The distribution of pathology grades in our cervix carcinoma cases is the reverse of that of the fundus cases.

TABLE IV. PATHOLOGIC GRADING

GRADE	CORPUS CASES		CERVIX CASES	
	NO.	PER CENT	NO.	PER CENT
I	321	40.7	127	11.2
II	211	26.8	363	32.0
III	140	17.8	414	36.5
IV	114	14.7	230	20.3

*Clinical Classification.*—This group of cases has been classified into three stages. Stage I includes those cases in which the disease is confined to the corpus regardless of the size of the uterus. Stage II includes those cases where there is extension beyond the corpus either to the cervix, one or both parametria, vagina, and/or distant metastases. Stage III includes those cases treated elsewhere prior to examination at this institution. These cases had been treated with radium, x-ray, surgery, either subtotal or total hysterectomy, or a combination of these three methods.

*Treatment.*—It will be noted that the cases herein reported cover a period of 30 years (1913 to 1942 inclusive). It is only natural that there have been numerous changes in the treatment technique and dosage during this period. In the earlier years only low voltage x-rays were available and the supply of radium limited. As a result the dosage from both x-rays and radium was low. Because of the very limited bed capacity of this institution at that period,

of 180 consecutive cervix malignancy cases are included in this table which shows an overweight for the cervix cases of 62.3 per cent. It is evident that the differences in overweight between the two groups becomes progressively greater with increasing overweight.

TABLE III.

	FUNDUS PER CENT	CERVIX PER CENT
Overweight	75.0	62.3
20 pounds or more	52.9	38.9
40 pounds or more	31.2	18.9
100 pounds or more	4.4	1.1

*Nationality.*—Several authors have commented on the fact that carcinoma of the fundus is more frequent in Jewish women than carcinoma of the cervix. Corsecaden and Gusberg<sup>5</sup> have stated that they found a "proportionate" number of Jewish women among those with cancer of the corpus, and Scheffey et al.<sup>9</sup> in their cases found that carcinoma of the fundus in Jewish women occurred more frequently than carcinoma of the cervix. They give 5.5 per cent occurring in Jews and 3.1 per cent in Negroes. In our group of 957 cases there were only two cases, 0.21 per cent, in Jews and only 3 cases or 0.31 per cent in Negro women. These figures would certainly suggest that corpus cancer is much less frequent in these races.

*Diabetes.*—The high incidence of coexistent corpus cancer and diabetes has been mentioned repeatedly. Scheffey et al.<sup>9</sup> reported 14 diabetics, or 11 per cent, among 127 cases of corpus cancer. Morse<sup>10</sup> reported a very high incidence of diabetics among his corpus cases; however, he used glucose tolerance tests rather than single fasting blood sugar determinations as the basis for his diabetic diagnosis.

In our 957 cases which cover a thirty-year period, routine blood sugar determinations were not done. In a subsequent group of 165 consecutive corpus cases, however, blood sugar determinations were made and it was found that there were 28 cases, or 16.9 per cent, of the patients who had fasting blood sugars above 120 mg. per cent and this blood sugar level together with glucose tolerance tests, history, and other findings, led to the diagnosis of diabetes.

This figure of 16.9 per cent diabetics has been compared with the results of a diabetic survey by Spiegelman and Marks<sup>11</sup> covering 1,300,399 females. The incidence of diabetes in the general female population over 35 years of age as reported in this survey is 1.02 per cent. Therefore, we find a ratio of diabetes in corpus carcinoma as compared with diabetes in comparable age groups of the general population as a whole to be 16.7:1.

The high incidence of overweight, late menopause, and sterility would seem to indicate some general endocrine imbalance, further substantiated by the high incidence of associated diabetes. Such an endocrine imbalance is thought to play a role in the etiology of corpus cancer.

*Hypertension.*—The high incidence of hypertension associated with corpus cancer has been mentioned elsewhere. It is most often mentioned because its presence is a contraindication to surgery. We have studied a large number of recent corpus cases and have found the incidence of hypertension above 140/90 to be 78 per cent. Comparing these findings with a study by Master et al.<sup>12</sup> of more than 6,000 women over 40 years of age, we find that their sample of the general population had hypertension, to the extent of 140/90 in 40 per cent of the cases at ages 40 to 49 and approximately 80 per cent of the cases at age 70 years. Since the majority of our cases fell in the sixth and seventh decades

The persistency of the disease following radiation was investigated in 86 surgical cases. These cases represent all of the Stage I radiated patients who were subsequently operated upon prior to 1948. The latter years were included in order to have as large a sample as possible and were used only to determine the relative number in which the disease was present at the time of operation. Of the 86, 45 were cases admitted between 1943 and 1947 and do not appear elsewhere in this study. Although the intracavitary radium dosage as expressed in milligram hours seems large as compared with the dosages used elsewhere, nevertheless, viable tumor cells were found in 69.7 per cent of the cases at the time of surgery. This compares with 49.6 per cent persistent disease after an average of only 3,600 mc. hr. of intracavitary radium as reported by Taylor and Becker<sup>7</sup> and 75.7 per cent with persistent disease as reported by Corsenden<sup>17</sup> of those cases which have been treated with 1,200 to 5,000 mg. hr. of intrauterine radium.

*Stage II.*—Since these cases represent the inoperable group a more intensive radiation program is arranged. This consists of radium tubes delivering the same dose as given in Stage I and in addition the same dosage of x-ray as given the nonoperated Stage I cases is delivered immediately upon completion of the radium treatment.

*Stage III.*—These cases, as stated above, represent secondary or previously treated cases; that is they have been treated elsewhere, by radiation, surgery or a combination of the two methods, prior to admission here. Many have had incomplete or subtotal hysterectomies with a short cervical canal remaining into which a suitable radium container cannot be inserted. Therefore, quite often the treatment in these cases is limited to external irradiation, usually as a palliative procedure. In cases previously treated with radiation only, where there is an adequate canal, the treatment is similar to the radiation given to the primary cases, although the amount of radiation previously administered and the interval between treatments will have a limiting effect on the amount of treatment that can be given safely. Where the disease is still confined to the uterus and where the patient is a suitable surgical risk, we feel that such a patient has a much better chance of survival if a hysterectomy is performed following the secondary radiation treatment. If there is extension beyond the fundus to the cervix or parametria or distant metastases, no surgery will be performed or recommended, and supplemental external radiation will be given in hope of obtaining additional palliation and in rare cases even a clinical cure.

*End Results.*—The end results of treatment regardless of the method used are presented in Table V. These results cannot be compared satisfactorily with the end results obtained by other clinics because of the difference in clinical classifications. The 32.6 per cent absolute cure rate in Stage III is essentially the same as that of the entire group and would suggest that the treatment given elsewhere, before the initial examination here, coupled with the fact that many of these cases represent recurrent activity of the disease, did not appreciably effect the end results in this stage.

TABLE V. FIVE-YEAR END RESULTS

STAGE	NUMBER ADMITTED	NUMBER TREATED	NO EVIDENCE DISEASE	DIED DISEASE	DIED OTHER CAUSES	LOST	CURE RATE	
							ABSO- LUTE PER CENT	RELA- TIVE PER CENT
I	437	425	189	190	34	12	43.3	44.5
II	225	222	22	185	14	1	9.8	9.9
III	295	274	96	160	8	10	32.6	35.1
Total	957	921	307	535	56	23	32.1	33.3

practically no surgery for corpus cancer was performed here and only a small percentage of the operable cases were subsequently subjected to surgery elsewhere.

During the next decade, 200 kv. x-ray therapy became available, as well as radon tubes and seeds. Heavier filtration of the intracavitary tubes plus increased penetration of the x-rays resulted in a larger dose to the tumor-bearing area. The x-radiation treatment was of the so-called "massive" dose technique, that is, the entire dose was administered in one or two treatments and as a result the amount of radiation delivered to the tumor was comparatively small.

From 1930 to 1940, radium element intracavitary tubes and fewer radon seeds were used. The average dose delivered by the radium tubes and seeds to a point 2 cm. lateral to the uterine canal was 3,200 r $\gamma$  and to a point 5 cm. lateral to the canal, 625 r $\gamma$ . The x-ray technique, too, was altered from the single massive dose to that in which daily increments were delivered over a period of several days. This resulted in increased dosage to the tumor-bearing area, the average x-ray dose being 1,200 r. throughout the pelvis.

During the years 1940, 1941, and 1942, the x-radiation technique changed in two ways: (1) 400 and 1,000 kv. generators were added, making available higher qualities of radiation, 5.0 and 9.0 mm. Cu. half value layer; and (2) a more pronounced protraction of the radiation over longer periods of time, usually several weeks. Thus doses of 3,000 to 4,000 r. were delivered to the tumor area, by means of x-rays alone. When possible, radium intracavitary tubes were introduced delivering doses of 4,000 to 5,000 r $\gamma$  to the 2 cm. point and 1,000 to 1,400 r $\gamma$  to the 5 cm. mark. The increase in dosage delivered was possible because the radium content of the individual units had been decreased. It was during this same period, because of hospital expansion, that an increase in surgical intervention took place subsequent to radiation.

In recent years several authors including Heyman,<sup>13</sup> Nolan and Arneson,<sup>14</sup> Martin,<sup>15</sup> and Schmitz<sup>16</sup> have shown improved end results by packing the uterine cavity with radium tubes over the results obtained by utilizing straight tandem tubes. While we have had no experience with this method and cannot compare end results, we do intend using it where surgery cannot be used.

The present procedure in the handling of fundus cancer at this institute is as follows:

*Stage I.*—Intracavitary tandem radium tubes (1 mm. platinum and 1 mm. steel filtration) are inserted into the uterine canal and left in position until a dose of from 5,400 to 6,700 r $\gamma$  are delivered to a point 2 cm. lateral to the canal. The tandem tubes are adjusted in length to radiate the entire length of the canal and are filled with radium cells having 1 mg. of radium per ml. length. The time of exposure is usually 100 hours or, in terms of milligram hours, varies from 4,500 to 9,000.

If the case is a suitable risk and the recommendation for surgery is accepted by the patient, a total hysterectomy and bilateral salpingo-oophorectomy are performed six weeks later. If the patient is not suitable for surgery or refuses it, supplementary x-ray treatments are substituted. An endeavor is made in these cases to deliver 3,000 to 4,000 r. into the uterus and broad ligament areas. The combined radium and x-ray dose at a point 2 cm. lateral to the center of the canal varies from 8,400 to 9,700 r., while at 5 cm. lateral to the same point the dose varies between 4,100 and 4,900 r.

Following this type of combined radiation treatment, the patient is examined in three months. If there are persistent symptoms and a repeat diagnostic dilatation and curettage show active tumor cells, additional intracavitary radium treatment is given, approximating two-thirds of the original intracavitary dose.

A further comparison may be made from Table VII. When the group operated upon is divided into two groups according to the type of surgery, whether total hysterectomy with salpingo-oophorectomy or subtotal hysterectomy, the former shows 80 per cent and the latter only 33.3 per cent absolute cure rate, thus further stressing the oft-repeated advice that a total operation should always be performed if possible, and there are very few cases where the total operation cannot be accomplished in Stage I cases.

In a previous publication by two of the authors<sup>18</sup> it was demonstrated that the age of the patient with carcinoma of the cervix uteri was influential in the course of the disease, or in other words that a better prognosis was associated with the more advanced age of the patient. A similar study was made of the fundus cases reported in this paper. All stages of the disease were considered collectively in determining the five-year cure rate in the different age groups. The indeterminate group consisting of all cases who died of other causes, who were lost within the five-year period, or who were not treated here, was eliminated because a comparative study only was being made. The patients were grouped in decades, but due to the small numbers in the early decades the second, third, and fourth decades were considered collectively. Similarly, the last two decades were combined. The results of this comparative study are shown in Table VIII, from which it is evident that contrary to the findings in carcinoma of the cervix, there is a progressively poorer survival with increasing age in carcinoma of the fundus.

TABLE VIII. FIVE-YEAR END RESULTS ACCORDING TO AGE

AGE	NUMBER ADMITTED	NO EVIDENCE DISEASE	DIED DISEASE*	5 YEAR SURVIVAL FREE OF DISEASE PER CENT
10-39	49	30	16	65.2
40-49	109	52	57	47.7
50-59	308	123	185	39.9
60-69	294	90	204	30.6
70-	90	15	75	16.7

\*Those cases alive with disease in the fifth year were included with the failures.

Weight, on the other hand, showed no effect on the ultimate results. The survival free of disease for five years was relatively the same for those above and those below a normal weight level.

A comparison was also made on the survival of the married women as compared to the single women. It was found that the survival free of disease for all stages was 32.2 per cent for the single women and 37.0 per cent for the married. This difference, because of the small sample of single women, is without significance.

The response of tumors to treatment is frequently associated with the degree of differentiation of the cells. In Table IX the five-year end results by clinical stages are presented for the combinations of Grade I with II and Grade III with IV. It is evident from this table that the more differentiated tumor group shows a markedly better response to treatment than the more anaplastic group. This was found to be true for all stages of the disease and the cure rates for the two groups differ significantly. This observation is in agreement with Taylor and Becker<sup>7</sup> who showed a cure rate in all clinical groups of 47.2 per cent in pathological Grades I and II combined and 22.8 per cent in pathological Grades III and IV combined. Bowing and Fricke<sup>19</sup> showed a cure rate for all clinical stages of 79.0 per cent for pathological Grade I, 33 per cent for Grade II, 25 per cent for Grade III, and 12 per cent for Grade IV.

It seemed advisable, however, to determine the effect on end results of the various changes in methods of treatment instituted throughout the years, as mentioned earlier under the heading *Treatment*. The cases, therefore, were arranged chronologically into the various year brackets. The end results were computed for each bracket based on the number free of disease in relation to the number treated, and are shown in Table VI.

TABLE VI. FIVE-YEAR END RESULTS ARRANGED CHRONOLOGICALLY

YEAR	NUMBER ADMITTED	NUMBER TREATED	NO EVIDENCE DISEASE	DIED DISEASE	DIED OTHER CAUSES	LOST	CURE RATE	
							ABSO- LUTE PER CENT	RELA- TIVE PER CENT
1916-1920	8	7	2	4	0	1	25.0	28.6
1921-1930	182	176	50	109	14	3	27.4	28.4
1931-1939	556	531	172	319	30	10	30.9	32.3
1940-1942	211	207	83	103	12	9	39.3	40.0

From this table it is evident that the end results improved in the more recent years. A slight improvement is shown in the 1931 to 1939 group over that of the 1921 to 1930 group. However, the better end results of the 1940 to 1942 group as compared with the 1931 to 1939 group is more impressive and could be attributed either to improved radiation technique and higher dosages or to the increased utilization of surgical procedures following radiation.

In order to investigate this problem, all Stage I cases from 1934 to 1942 having had surgical intervention subsequent to radiation were compared with Stage I cases having had radiation only. The years 1934 to 1942 were selected because prior to 1934 there were no Stage I cases operated upon in this series, and thus we are enabled to compare the groups for the same period of years. These data are shown in the upper half of Table VII. As can be observed, the nonoperative Stage I cases for the years 1940 to 1942 showed no better end results than for the preceding period. From this we conclude that the greater radiation doses delivered in the latter three years were still inadequate to cope with the disease in a large percentage of the cases.

TABLE VII. ALL STAGE I CASES, 1934-1942

	NUMBER AD- MITTED	NUMBER TREAT- ED	5 YEAR NO EVI- DENCE DISEASE	DIED DISEASE	DIED OTHER CAUSES	LOST	CURE RATE	
							ABSO- LUTE PER CENT	RELA- TIVE PER CENT
<i>Radiation Only.</i> —								
1934-39	200	192	82	91	15	3	41.0	42.7
1940-42	80	80	33	36	8	3	41.3	41.3
Total	280	272	115	127	23	6	41.1	42.3
<i>Radiation Plus Surgery.</i> —								
Total hys- terectomy	30	30	24	4	0	2	80.0	80.0
Subtotal hys- terectomy	9	9	3	5	0	1	33.3	33.3
Total surg- ical cases	39	39	27	9	0	3	69.2	69.2

Comparison of the over-all survival of the operative group with the non-operative cases indicates that there is a significantly greater survival in the group operated upon. Since the radiation alone was productive of no improvement and since operation subsequent to radiation does show a marked improvement, we conclude that the second procedure is the method of choice.



Taylor and Becker<sup>2</sup>:

*Stage I.*—No enlargement, no extension beyond the fundus.

*Stage II.*—Enlargement without fixation or metastases:

(a) less than 2½ months' pregnancy in size;

(b) more than 2½ months' pregnancy in size but still freely movable.

*Stage III.*—Clinical evidence of extension beyond the fundus itself:

(a) extension to cervix only;

(b) extension to vagina, parametrium, adnexae, and distant metastases.

Miller and Henderson<sup>21</sup>:

*Stage I.*—No palpable enlargement of the uterus.

*Stage II.*—Moderate enlargement of the uterus to size of 2½ months' pregnancy.

*Stage III.*—Uterus greater than a three months' pregnancy.

## American College of Surgeons:

Primary Cases A. Limited to uterine body.

B. Involvement of broad ligaments.

C. Vaginal metastases.

D. Metastases regional.

E. Metastases remote.

It will be seen from the above that some classifications stress the size of the uterus more than any other factor and indicate that this is more important than extension of the disease beyond the corpus. We cannot agree that this is true. Even if the size of the uterus is as important as some authors indicate, we feel that it is often difficult and sometimes impossible accurately to determine the size of the uterus, since these patients are often extremely obese; even if the uterus is considerably enlarged, it cannot be felt through the obese abdominal wall. We further maintain that the measurement of the uterine canal with a sound will not give accurate indication of the size since the wall of the uterus varies markedly in its thickness and the associated leiomyomas would render this type of measurement inaccurate. We feel that it is often impossible to make a preoperative determination of the size of the uterus accurately enough to state that the uterus is or is not enlarged, and if enlarged whether to the size of a 2½ months' pregnancy or larger. Some of our operative patients have weighed over 300 pounds and many weigh more than 250 pounds.

Crossen<sup>21</sup> has used factors in a clinical classification which obviously cannot be determined clinically, but can be determined only after the uterus has been removed and sectioned. Parts of his classification are obviously worthless in any except operative cases and if preoperative radiation is used it is worthless in these operative cases, since the changes following irradiation are so variable as to be unpredictable.

Three of the above authors, Miller and Henderson,<sup>22</sup> Taylor and Becker,<sup>7</sup> Bowing and Fricke,<sup>19</sup> and others have shown by statistics that the end results are definitely influenced by the pathological grades of the tumors when their entire group of cases is considered for pathological grading only. This paper shows that this belief holds true even when the cases are divided into their clinical groups.

As far as we have been able to determine from the literature, pathological grading has not been used as a factor in classification. This may be because the classification is clinical and pathological grading should not be considered. However, it is felt that anything that has such a definite influence on the end results should be considered in the clinical classification.

Although the pathological grade of the tumor as shown above has a very definite and marked influence on the cure rate in corpus carcinoma, we have been unable to find any such influence of pathological grading on 1,134 cases of cervix carcinoma or on 147 cases of vulvar carcinoma. Smith and Pollack<sup>20</sup> did show some similar influence in their group of vulvar carcinomas, but the number of cases used to substantiate their opinion was too small to make the results significant.

TABLE IX. FIVE-YEAR END RESULTS ACCORDING TO PATHOLOGIC GRADE

PATHOLOGIC GRADES I AND II					PATHOLOGIC GRADES III AND IV			
CLINICAL STAGE	NUMBER	NO EVI-DENCE DISEASE	DIED DIS-EASE*	SURVIVAL PER CENT	NUMBER	NO EVI-DENCE DISEASE	DIED DIS-EASE*	SURVIVAL PER CENT
I	249	136	113	54.6	104	37	67	35.6
II	119	16	103	13.5	75	2	73	2.7
III	120	50	70	41.6	54	12	42	22.2
Total	488	202	286	41.4 ± 2.23%	233	51	182	21.9 ± 2.71%

\*Includes those cases alive with disease in the fifth year.

Discussion of Clinical Classifications

There are so many different clinical classifications in existence, using entirely different criteria, that it is impossible to correlate end results from the different clinics using these various methods of clinical classification, or to evaluate the effect of types of therapy on end results. Our classification has been given earlier in this paper and we are listing below several classifications taken from the literature to illustrate the many factors which various clinics consider important.

Crossen<sup>21</sup>:

- Stage I.—The tumor is limited to the surface endometrium and shows no invasion of the muscular layer.
- Stage II.—Definite involvement of muscular layers, limited to the inner half of the myometrium.
- Stage III.—Extension to the outer half of the myometrium, including possible invasion of the serosa.
- Stage IV.—Extension of the tumor outside of the uterus in the parametrium, or the existence of an operable metastatic implant in the ovary.
- Stage V.—Extension to adjacent removable organs, verified microscopically.
- Stage VI.—Regional extension or distant metastases beyond the scope of surgical removal.

Bowing and Fricke<sup>19</sup>:

- Stage I.—The uterus is not enlarged and is freely movable.
- Stage II.—Uterus is enlarged but still freely movable.
- Stage III.—(a) Uterus is not enlarged but with limited mobility and infiltration of the entire parametrium.  
 (b) Uterus is enlarged and fixed with infiltration of the entire parametrium out to the pelvic wall.  
 (c) Uterus is enlarged or not, with involvement of the cervix with or without vaginal invasion.
- Stage IV.—Uterus enlarged and fixed; evidence of extrapelvic metastases.

## PREGNANCY WITH SICKLE CELL ANEMIA

### Review of the Literature and Report of Cases

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WHILE the acute hemolytic crisis of sickle cell disease is not rare, its occurrence in pregnancy has seldom been reported. In a review of the literature, we have found only 23 such cases recorded.<sup>1-14</sup> The review by Kobak, Stein, and Daro<sup>7</sup> is an excellent one. However, several of the cases included appear to be examples of the nonhemolytic form which seems to have little effect on pregnancy.<sup>15</sup> The cases reported since that time<sup>1-14</sup> and the six cases we wish to report bring the total number to twenty-nine. Because of the paucity of recorded material, these are described in detail in order to make available in the literature material for future evaluation.

CASE 1.—(No. 15117). The patient was a nineteen-year-old Negro woman, who had been found to have sickle cell anemia two years before. She had been followed in the Out Patient Clinic, where it was noted she had persistent anemia accompanied by clinical icterus, with icterus indices ranging from 21 to 30 units. Four years before the present hospital admission, the patient had had an abortion at six months' gestation, the cause of which was not known. Three weeks prior to admission, there were weakness and shortness of breath on exertion which became progressively worse, and admission to the hospital was sought. She gave a history of amenorrhea of seven months' duration.

Temperature on admission was 98.6° F., pulse 110, respirations 25, and blood pressure 120/70. Dyspnea was marked, the sclerae were icteric, and there were moist râles in the left lung base. The heart was enlarged to the left with a loud, blowing systolic murmur over the entire precordium. There was uterine enlargement consistent with a pregnancy of seven months' duration. Fetal heart tones were good. There were shallow, punched-out ulcers about both ankles with slight pitting edema of the lower legs.

Laboratory work showed a red blood count of 0.69 million and hemoglobin of less than 7 Gm. per cent (patient died before studies were completed). There was 100 per cent sickling of the red cells at twelve hours. The urine showed a moderate amount of albumin.

Transfusion was started, but when approximately 100 c.c. had been given, she had a severe pyrogenic reaction accompanied by marked dyspnea. The transfusion was discontinued, and she was given morphine sulfate, 10 mg. The lungs were clear to physical examination at the time. Suddenly respirations ceased, and she was pronounced dead two hours after admission. The fetal heart tones were not heard shortly before death.

The blood was retyped and cross-matched several times after death to rule out laboratory error in compatibility.

Necropsy showed 200 c.c. of fluid in each pleural cavity and 250 c.c. of fluid in the pericardial sac. The heart weighed 360 Gm. Its musculature was flabby and pale. There were no abnormalities of the vessels or valves. The lungs showed acute congestion and edema.

## Summary

1. Nine hundred fifty-seven cases of corpus cancer are considered and end results are given for the entire group and for each clinical classification.

2. It is definitely shown that total hysterectomy and bilateral salpingo-oophorectomy following preoperative radiation produce the best cure rate.

3. Various clinical classifications are discussed, none of which seems entirely satisfactory and it is thought that some clinical classification employing all of the factors which influence the end results should be adopted, so that the end results from the various clinics could be compared and evaluated.

4. Comments are made on the high incidence of diabetes, overweight, late menopause, and sterility among corpus cancer patients, and the low incidence of corpus cancer among Jewish and Negro women.

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CASE 3.—(No. 8660) This twenty-two-year-old Negro gravida iii, para ii, was admitted to the hospital with the chief complaint of pain in the legs and chest of two weeks' duration. The past history was noncontributory. Her two previous pregnancies had been normal with spontaneous delivery at term. Both children were alive and well at the time of admission, but were not available for study.

The patient complained of ankle edema, orthopnea, and a painful, nonproductive cough. There was amenorrhea of eight months' duration.

Temperature on admission was 99.6° F., respirations 20, pulse 88, and blood pressure 184/50. The sclerae were icteric. The heart was enlarged to the left with a soft systolic murmur over the precordium. The fundus of the uterus reached the manubrium. There was a 2 plus pitting edema of the ankles as well as pigmented scars on the lower legs.

Laboratory data showed red blood count 2.4 million, hemoglobin 4.5 Gm., white blood count 9,230 with 83 per cent polymorphonuclear leucocytes; the smear showed 6 per cent nucleated red cells. There was 3 per cent immediate sickling with 90 per cent sickling in twelve hours. The urine showed a persistent albuminuria with maximum specific gravity of 1.012. Icterus index 18 units.

The patient was put to bed and given a high vitamin, salt-free diet. She was also given iron and transfused four times with 500 c.c. of whole blood. The blood pressure steadily dropped until it was within normal limits, but the albuminuria persisted. The hemoglobin reached 8.5 Gm. On the twenty-second day, labor was induced with quinine and Pitocin. After an hour of active labor, she spontaneously delivered a term infant in good condition. The postpartum course was uneventful, and the patient was discharged in good condition four days after delivery.

The patient was admitted three years later in the seventh month of pregnancy. She had been seen three months before when her pregnancy was discovered. Her hemoglobin was 8 Gm. and her red cell count was 3.8 million and she had no complaints. She had been examined periodically in the Out Patient Clinic since that time.

When she was admitted she was complaining of intermittent pain in the lumbosacral region. The history was otherwise negative.

Temperature on admission was 98.6° F., respirations 20, pulse 80, and blood pressure 120/75. The sclerae were markedly jaundiced. The heart was enlarged to the left with a blowing systolic murmur heard over the entire precordium. The fundus of the uterus was 27 cm. above the symphysis pubis. The fetus was active and fetal heart tones were good. The remainder of the physical examination was noncontributory.

Laboratory data showed red blood count of 2.34 million, hemoglobin of 2.5 Gm., white blood count of 10,200, with 90 per cent polymorphonuclears, 4 per cent lymphocytes, 6 per cent eosinophiles. There were 30 per cent nucleated red cells, and 9 per cent reticulocytes. There was 15 per cent immediate sickling in the sealed wet smear. The icterus index was 14.4 units. An electrocardiogram showed changes consistent with myocardial damage.

She was digitalized and daily transfusions of 250 c.c. of whole blood were given. After receiving 3,250 c.c. of blood, the hemoglobin increased to only 7.5 Gm. per cent. She was free of symptoms during this period. On the thirteenth hospital day, her temperature suddenly rose to 104° F. The sclerae appeared more icteric, but physical examination was otherwise negative. The white blood count was 28,000 with 92 per cent polymorphonuclears, and 2 per cent nucleated red cells. The hemoglobin was 7.5 Gm. per cent. Icterus index was found to be 42 units. The urine showed 4 plus albuminuria with a moderate number of granular casts. X-ray of the chest was negative. The next afternoon the patient complained of slight pain in the left lower quadrant, and one hour later spontaneously delivered a premature female infant in good condition. The elevated temperature continued. The icterus index reached 57 units, and the blood urea nitrogen 90 mg. per cent. However, the urinary output remained over 1,000 c.c. in twenty-four hours. On the first postpartum day the respirations increased to 40 per minute and crackling râles were noted in the right base. The icterus index had risen to 176 units and the hemoglobin had dropped to 4.5 Gm. per cent. She

The liver was enlarged with accentuation of the vascular pattern. The spleen was a small fibrotic structure, weighing slightly less than 2 Gm. The kidneys showed glomerular engorgement with numerous small red dots in the cortical areas.

Histologic examination showed widespread sickling, the vessels being stuffed with agglutinated masses of these cells which appeared to form actual thrombi, notably in the heart, kidneys, and lungs. The myocardium showed degeneration and possible early necrosis with interstitial and intravascular cellular reaction consisting chiefly of polymorphonuclear leucocytes. There was an erythroblastic hyperplasia of the bone marrow. Extramedullary hematopoietic foci were present in the liver.

Necropsy of the infant which weighed 1,900 Gm. showed no evidence of sickling within the fetal tissues.

CASE 2.—(No. 2603). This sixteen-year-old Negro primigravida came to the Out Patient Clinic six months prior to death. A diagnosis of sickle cell anemia was made, but she declined admission to the hospital. Two months later in the Obstetrical Clinic, she was found to be six months pregnant, and was admitted at this time.

Laboratory data showed a red blood count of 1.75 million, hemoglobin 4 Gm. per cent; white blood count 10,000 with 79 per cent polymorphonuclear leucocytes and 19 per cent lymphocytes. The smear showed 5 per cent nucleated red cells. There was 15 per cent immediate sickling in the sealed wet smear. Van den Bergh reaction was 1 plus indirect. Urinalysis was negative.

Three transfusions of 500 c.c. each were given and the hemoglobin increased from 2 to 6 Gm. per cent, and she was discharged after 32 days to the Out Patient Clinic. Two weeks after discharge, she noticed edema of the ankles which increased rapidly and soon involved the legs and the lower abdominal wall. She was readmitted one month later.

Physical examination showed temperature 100° F., pulse 120, respirations 22, and blood pressure 180/100. There was marked dyspnea and distention of the neck veins. The sclerae were icteric. There were moist râles in both lung bases. The heart was enlarged to the left. The fundus of the uterus was 6 cm. above the umbilicus. Fetal heart tones were audible. There was pitting edema of the legs and thighs.

Laboratory data showed red blood count 1.4 million, hemoglobin 3.7 Gm. per cent, white blood count 36,500 with 75 per cent polymorphonuclear leucocytes, 17 per cent lymphocytes, 6 per cent mononuclears, and 2 per cent eosinophiles. There were many nucleated red cells. Blood urea nitrogen was 17 mg. per cent.

An electrocardiogram showed inversion of P<sub>1</sub> and T<sub>1</sub>, low voltage of T<sub>2</sub>, T<sub>3</sub>, and T<sub>4</sub>, findings which were thought compatible with myocardial damage.

She was given 400 c.c. of whole blood intravenously and six hours later she became comatose and failed to respond to stimulants, expiring 20 hours after admission. Since fetal heart tones were not heard during the last four hours, a postmortem section was not done.

Necropsy showed bilateral hydrothorax, hydropericardium, and ascites. The heart weighed 600 Gm. Its ventricular chambers were dilated with flattening of the trabeculae carneae and papillary muscles. The myocardium was flabby and pale. There were no lesions of the valves or coronary arteries. The lungs were acutely congested, with much edema fluid in the lower lobes. The liver, mediastinal, and mesenteric lymph nodes were enlarged. The spleen weighed 95 Gm. The kidneys were swollen and pale. The uterus was enlarged and contained a fetus weighing 1,675 Gm.

Histologically, there was generalized vascular engorgement with variable degrees of sickling throughout the body. Sickling was prominent in the leptomeningeal vessels. Sick cells were also present in the maternal portion of the placenta. The bone marrow was hyperplastic with increased erythroblastic activity. The spleen was packed with erythrocytes and contained focal areas of fibrosis with deposits of greenish-black pigment. Erythrophagocytosis within the spleen and lymph nodes was evident.

Examination of the fetus showed profound vascular engorgement, but no evidence of sickling.

Icterus index was 27 per cent. There was 75 per cent sickling in forty-eight hours. Repeated urinalyses showed a persistent albuminuria, the highest specific gravity recorded being 1.013.

After a twenty-seven-hour labor, the patient spontaneously delivered a full-term infant in good condition. There was puerperal morbidity for two days. The postpartum course was otherwise normal, and she was discharged in good condition on the seventeenth postpartum day.

She was again admitted three years after her first admission, in labor. The three years between admissions had been uneventful. The patient was seen on two occasions in the Prenatal Clinic. In the sixth month her hemoglobin was 8 Gm. and in the seventh month 5 Gm. She did not return to the Prenatal Clinic again.

On admission, temperature was 100.6° F., pulse 120, respirations 20, and blood pressure 125/80. There was a systolic murmur over the entire precordium. The uterus was the size of a term pregnancy. The fetal heart tones were good. Uterine contractions were irregular and there was no cervical dilatation.

Laboratory data showed red blood count of 0.9 million, hemoglobin 3 Gm., white blood count 18,525 with 92 per cent polymorphonuclears; the smear showed 5 per cent nucleated red blood cells. There was 1 per cent immediate sickling with 100 per cent sickling in forty-eight hours. Icterus index was 18 units.

The patient was in false labor. She was given four transfusions, and the hemoglobin reached 5.5 Gm. On the ninth hospital day, labor was induced by rupture of the membranes. A normal infant was delivered. Postpartum course was uneventful, and the patient was discharged in fair condition on the twentieth postpartum day.

CASE 6.—(No. 62685). This nineteen-year-old gravida ii was first seen in the Out Patient Clinic two weeks prior to admission, complaining of tingling and numbness in the fingers and toes, headaches, and epistaxis of one week's duration. On admission to the hospital, these symptoms had ceased, but she was complaining of general weakness and pain under the left breast and severe pain in both shoulders, the neck, and upper dorsal spine. She had been in bed since her last clinic visit. Her first pregnancy had resulted in an abortion at six months, otherwise her past history was one of good health.

On physical examination, temperature was found to be 98.6° F., pulse 84, respirations 16, and blood pressure 132/82. She was an acutely ill, emaciated Negro woman with an intrauterine pregnancy of approximately seven months. Fetal heart tones were good. There were definite neck rigidity, tenderness to palpation across the shoulder girdle and along the entire length of the spine. Reflexes were physiological. There was a soft murmur over the entire precordium. Physical examination was otherwise negative.

Laboratory data on admission and throughout her hospital stay are shown for the most part in Fig. 1. There was 5 per cent immediate sickling and 90 per cent sickling in twenty-four hours. Urinalysis was negative. Repeated examinations showed a negative spinal fluid except that proteins were persistently above 100 mg. X-rays of the skull, spine, and chest were negative. Electrocardiograms showed sinus arrhythmia. Mantoux, Wassermann, and Kline tests were negative. A Frei test showed a 2 plus reaction.

Symptomatic and supportive therapy were given in the form of high-calorie, high-vitamin diet, iron medication, and anodynes. She was confined to bed during the greater part of her hospital stay. There were frequent exacerbations of her symptoms, but the neck rigidity and tenderness persisted. Weakness and inability to move about without discomfort were marked. The pregnancy apparently proceeded normally with no suggestion of premature labor or fetal difficulty. Ten days before her estimated date of confinement, labor began spontaneously. After thirty-six hours, the patient spontaneously delivered a 5 pound, 7 ounce infant in good condition. Increased blood destruction during the course of labor was shown by a series of icterus indices at four-hour intervals, the highest titer being 33 units. The postpartum course was uneventful. All symptoms ceased, and the neck rigidity disappeared shortly after delivery. The patient was up and about the ward on the fourth

pursued a steady downhill course with respirations increasing to 60 per minute, and the pulse to 130. Terminally the pulse and respiration seemed to cease at almost the same instant. Death occurred early in the morning of the second postpartum day, or on the seventeenth hospital day. Permission for necropsy could not be obtained.

The red cells of the child were examined, and 3 per cent sickling was found in twenty-four hours.

CASE 4.—(No. 42802). This twenty-five-year-old multigravida had been twice previously delivered in the hospital. On her first admission she was a primigravida in early labor. Hemoglobin at this time was 7.5 Gm., and the icterus index 25 units. There was 85 per cent sickling of the red cells in 24 hours. She received a transfusion of 500 c.c. of whole blood. After thirty-seven hours of labor, delivery was effected by midforceps. There was puerperal morbidity of five days' duration, during which she received two more transfusions of 500 c.c. each. She and the infant were discharged in good condition on the tenth postpartum day.

On her second admission she was in active labor. The prenatal course had been uneventful. There had been no fetal movements for the past twelve hours, and no fetal heart tones were heard on physical examination. Hemoglobin was 7.5 Gm., sickling was again present. After sixteen hours of labor she delivered a stillborn, macerated infant with cord wrapped tightly around its neck. She was given one transfusion before discharge.

Between her second and third admissions, she delivered a normal, full-term infant in her home.

She was admitted for the third time four hours after spontaneously delivering a full-term infant in good condition, in her home, attended by the Out Patient Service. The patient had attended clinic infrequently in spite of frequent promptings. She did not follow instructions and refused admission even for delivery. She complained of weakness, fatigue, and difficulty in breathing.

On admission, temperature was 99.6° F., pulse 120, respirations 30, and blood pressure 104/70. Dyspnea was marked. There was a blowing systolic murmur at the apex. The fundus of the uterus was firm and at the level of the umbilicus.

Laboratory data showed a red blood count of .9 million, hemoglobin of 2.4 Gm., white blood count 20,000 with 92 per cent polymorphonuclears. The icterus index was 14.7 units. There was 1 per cent immediate sickling with 100 per cent sickling in forty-eight hours. Blood work was repeated after three transfusions and showed a red blood count of 2.1 million and hemoglobin of 5.07 Gm. The urine was negative.

Transfusion of 500 c.c. of whole blood was given shortly after admission and the dyspnea was completely relieved. Transfusions were given on the first and second days of the hospital stay, but not on the third day. She received another transfusion on the morning of the fourth hospital day. Late that afternoon the patient developed acute pulmonary congestion and some ankle edema. She was digitalized and given oxygen by nasal catheter. There was little response, and the patient expired seven hours after onset of the symptoms. Permission for necropsy was not granted.

The infant was found to have a red blood count of 5.8 million with a hemoglobin of 15 Gm. There was no sickling. He took nourishment well, gained weight rapidly, and was discharged in good condition.

CASE 5.—(No. 11970). This seventeen-year-old gravida i was first admitted to the hospital in 1944 in labor. She had been followed in the Obstetrical Clinic and was found to have persistent anemia, the etiology of which was undetermined at that time: Her past history was essentially negative.

Temperature on admission was 99.6° F., pulse 100, respirations 16, and blood pressure 132/82. There was a systolic murmur at the apex. Fetal heart tones were good.

Laboratory data showed a red blood count of 2.7 million, hemoglobin 5 Gm., white blood count 20,000 with 67 per cent polymorphonuclears. The reticulocyte count was 15 per cent.



From time to time, the blood destructive process appears to be accelerated and may be accompanied by episodes of aching and pain in the joints or extremities. There may be severe abdominal pain with accompanying prostration and muscular rigidity closely simulating one of the acute abdominal accidents requiring surgical intervention.<sup>22</sup> A clinical picture simulating coronary occlusion has been observed.<sup>23</sup> These episodes of apparent acceleration are sometimes referred to as "crises."

A previous study of sickle cell anemia associated with pregnancy<sup>17</sup> indicates that it produces little alteration from the normal during the course of pregnancy and the puerperium.

TABLE 1. COMPLICATIONS OF PREGNANCY AND DELIVERY IN PATIENTS WITH SICKLE CELL ANEMIA

CASE	DEATH OF MOTHER	STILLBORN	PREMATURE LABOR	TOXEMIA	MORBIDITY
1. Fouché and Switzer†	+				
2. ‡	+			+	
3. (A)	0	0	0	-	
(B)	+	0	+	+	+
4. (A)	0	0	0	0	+
(B)	0	+	0	0	0
(C)	+	0	0	0	0
5. (A)	0	0	0	-	+
(B)	0	0	+	0	0
6.	0	0	0	0	0
7. Yater & Mollari (1)*	+				
8. Richter, et al. (2)	0	0	0	0	+
9. Sharp & Schleicher (3)	0	0	0	0	0
10. Lewis (4)*	0				
11. Sodeman & Burch (5)	0	0	0	0	0
12. Page & Sifton (6)	0	0	0	0	0
13. ‡	+				
14. Kobak, et al (7)	+	+	0	0	0
15.	0	+	0	+	0
16.	0	0	+	+	+
17.	0	0	0	0	+
18. Van der Sar (8) (A)	0	+	+	0	0
(B)	0	0	0	0	0
19. Spivak (9)	0	0	0	+	0
20. Zimring (10)†	0	0	0	0	+
21. Noyes (11)‡	+			+	0
22. Martinak (12)†	0	0	0	0	+
23. Hodges & Bernstine (13)	0	0	+	+	0
24. (A)	0	0	0	0	0
(B)	0	0	+	0	0
25.	0	0	0	0	0
26. Carangelo & Otts (14)	+	0	+	0	+
27. (A)	0	0	0	0	0
(B)	0	0	0	0	0
28.	0	0	0	0	0
29.	0	+	0	0	0

\*Case 7 aborted spontaneously at 6 months. Case 10 was aborted therapeutically.

†In Cases 20 and 22 there was postpartum hemorrhage.

‡Died undelivered.

In a review of the literature, reports of only 23 definite instances of sickle cell anemia associated with pregnancy were found. All cases were excluded which did not show clinical or laboratory evidence of jaundice in addition to the sickling trait. In most accepted instances, there were also reported an increased reticulocyte count and the finding of normoblasts or other nucleated erythrocytes in the circulating blood, important presumptive evidences of a blood destructive type of anemia.

postpartum day, complaining only of slight weakness. She was discharged in good condition on the tenth postpartum day.

The infant showed no evidence of sickling in a series of sealed wet smears.

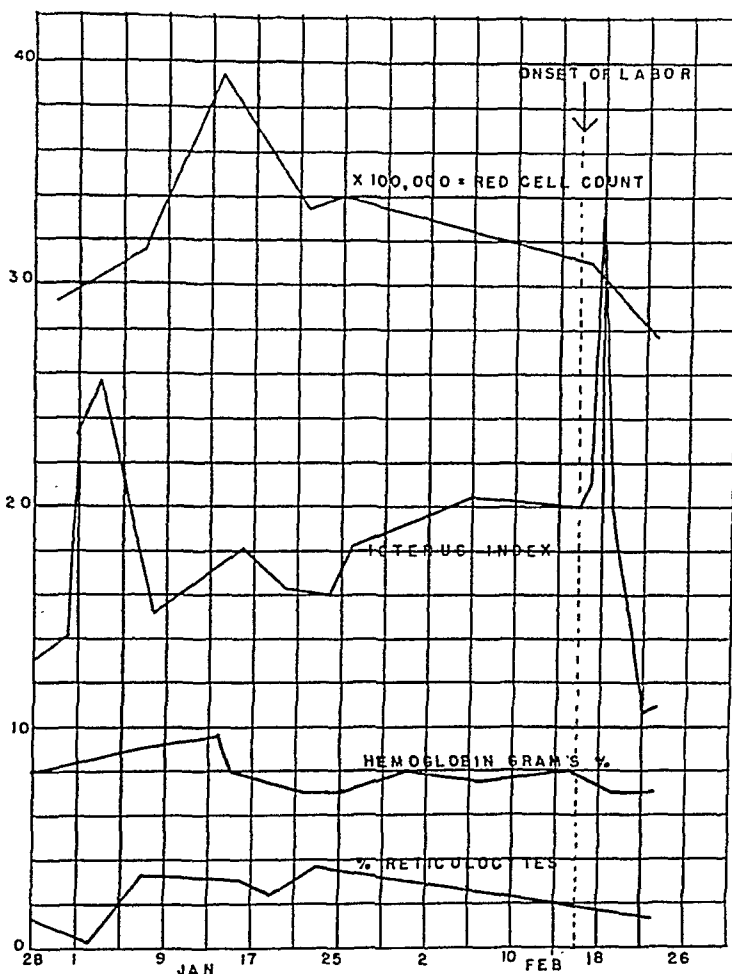


Fig. 1.—Graphic representation of laboratory findings in Case 6, showing sharp rise of icterus index with onset of labor.

### Discussion

Sickling of the red blood cells is an hereditary abnormality found in 7 to 14 per cent of American Negroes.<sup>15, 16, 17</sup> It is transmitted as a dominant Mendelian factor.<sup>18, 19, 20</sup> There are two forms of sickle cell disease: (1) sicklemia in which there is sickling of the cells, but no evidence of blood destruction or increased rate of regeneration and (2) sickle cell anemia in which there is not only sickling, but also active blood destruction and such evidence of increased regeneration as reticulocytosis and nucleated red cells. The ratio of sickle cell anemia to sicklemia has been estimated as from 1:9 to 1:40.<sup>15, 21</sup>

The relationship of the two forms is not clear. Some individuals with the trait are known to go through life without ever showing the anemia. However, if the active form develops, it usually begins in the first two decades of life and once the blood destructive process is activated it does not disappear. Wintrobe<sup>22</sup> reports that he has observed remissions, but never to the extent that there was no evidence of blood destruction.

the increased incidence of premature labor and stillbirths is obscure. Thrombotic phenomena often occur in other parts of the body in sickle cell anemia and may well occur in the fetal or maternal portion of the placenta, thereby precipitating these events. An explanation for the increased incidence of toxemia of pregnancy in these patients is likewise difficult to find. Renal damage may be suspected as being a factor in some instances.

In Table III it is shown that the most common cause of death in sickle cell anemia complicated by pregnancy is congestive heart failure.

The mortality, 31 per cent in these patients, is large and even though the prognosis for long life in the patient with uncomplicated sickle cell anemia is not good,<sup>7, 22</sup> it indicates that pregnancy is a severe additional strain.

Fig. 1 is a graphic representation of certain laboratory findings in Case 6. It indicates that the blood destructive process was accelerated with the onset of labor in this patient. There are no other studies available which would indicate that the onset of labor causes increased blood destruction in the patient with sickle cell anemia. Pregnancy itself does not seem to precipitate an active form of sickle cell disease in sickle cell women,<sup>17</sup> although 55 per cent of the reported cases of sickle cell anemia with pregnancy are in primiparas who give no history of previous blood destructive episodes. It is possible that a previously mild but active form of the disease which had been unnoticed becomes symptomatic in the presence of the added burden of pregnancy.

Sickling was observed in 5 of 16 children of mothers with sickle cell anemia, or 31 per cent of those examined in the course of the observations made by the various groups whose data we have analyzed in Table I.

The treatment of the patient with sickle cell anemia is unsatisfactory. There is no specific therapy. The use of iron, vitamins, and protein apparently influences the disease slightly if at all. The treatment that we consider most useful in the sickle cell patient with pregnancy is outlined in the following paragraphs.

**A. In Crisis.**—Multiple transfusions will provide a temporary supply of blood. This is directed primarily toward correction of the anemia and the relief of attendant symptoms. Because of the tendency of patients with sickle cell anemia to have reactions to transfusions<sup>22</sup> and to go into congestive heart failure, the blood must be given very slowly. It is probably wise to alkalize the patient's urine beforehand. It is also recommended that the blood be given in small quantities and at more frequent intervals than the usual 500 c.c. transfusion. Since the cause of death in these patients is so often a sudden onset of congestive heart failure, we believe that prophylactic digitalization is indicated.

**B. Not in Crisis.**—The use of multiple blood transfusions throughout the last trimester and before the onset of labor has been recommended by Spivak.<sup>9</sup>

1. In light of the present knowledge concerning the reaction of sickle cell anemia patients to operative procedures, it is questionable in our minds as to which is the procedure of choice: (a) termination of pregnancy by therapeutic abortion or (b) attempting to carry the patients to the stage of fetal viability. Since these patients do seem to have at least a temporary improvement once they are delivered, induction of labor as soon as the fetus is viable may be advisable. If the patient with a past history of hemolytic crises is seen in the early stages of pregnancy and the disease is in the inactive or latent phase, therapeutic abortion should be seriously considered.

2. A decrease in oxygen tension causes an increase in sickling of the red blood cells<sup>30</sup> with increased viscosity and possibly localized or generalized

Complications of pregnancy and delivery in the 29 patients available for study have been summarized in Table I.

As shown in Table II, there is an increase in the incidence of major complications of pregnancy and labor in patients who have sickle cell anemia with the exception of postpartum hemorrhage and abortion.

TABLE II. INCIDENCE OF COMPLICATIONS OF PREGNANCY IN SICKLE CELL ANEMIA PATIENTS AS COMPARED WITH OTHER GRAVID WOMEN

	AVERAGE AS REPORTED IN STANDARD TEXTS (PER CENT)	SICKLE CELL ANEMIA PATIENTS (PER CENT)
Anemia (hemoglobin)	66 <sup>24</sup>	37.4
Postpartum hemorrhage	5-7 <sup>25, 26</sup>	5.5
Premature labor	2.95 <sup>27</sup>	19.4
Stillbirths	2.41 <sup>28</sup>	13.8
Morbidity	10.5 <sup>28</sup>	25
Abortion	20 <sup>28</sup>	10.8
Toxemia	10 <sup>28</sup>	25

TABLE III. REPORTED CAUSE OF DEATH IN PATIENTS WITH SICKLE CELL ANEMIA AND PREGNANCY

CASE	CLINICAL IMPRESSION	AUTOPSY FINDINGS
1. Fouché and Switzer	Transfusion reaction; congestive heart failure	Marked sickling. Pericardial effusion, myocardial dilatation and hypertrophy. Myocardial degeneration, congestion of lungs, hepatomegaly. Atrophy of spleen. Passive congestion of liver and kidneys.
2. Fouché and Switzer	Congestive heart failure	Marked sickling, generalized edema, bilateral hydrothorax, hydropericardium, ascites. Cardiac hypertrophy and dilation, enlarged liver.
3. Fouché and Switzer	Sickle cell crisis broncho-pneumonia	Autopsy not obtained.
4. Fouché and Switzer	Congestive heart failure	Autopsy not obtained.
7. Yater and Mollari <sup>1</sup>	So-called abdominal crisis—thrombosis of hepatic arteries?	Enlarged liver, hydroperitoneum, hydropericardium, heart dilated, hypertrophied, atrophy of spleen, old infarcts of spleen and kidney.
13. Page and Silton <sup>6</sup>	Bronchopneumonia; anemia	Hemorrhagic infarcts in lungs; early bronchopneumonia, pelvic phlebotrombosis
14. Kobak, et al. <sup>7</sup>	Pneumonia	Marked sickling, enlarged liver and spleen. Myocardial degeneration. Atelectasis of lungs. Passive congestion of liver, spleen, and kidneys.
21. Noyes <sup>11</sup>	Congestive heart failure. Toxemia of pregnancy.	Marked sickling. Right-sided heart failure, pleural effusion, visceral congestion.
25. Carangelo and Otts <sup>14</sup>	Overwhelming renal infection	Bilateral medullary abscesses of both kidneys. Severe icterus.

The increase in morbidity is best explained by the decreased resistance of these patients to infections because of the severe anemia. However, it must be remembered that in sickle cell anemia spontaneous thrombosis and infarction are frequent with subsequent fever and leucocytosis. The cause of

## THE ATTITUDE OF THE FETUS IN BREECH PRESENTATION

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IN RECENT years, the trend toward reduction in the maternal and fetal mortality has been quite marked. However, the fetal mortality rate in breech deliveries is much too high. This study is made to determine the results of the management of breech deliveries since the opening of the Woman's Clinic of the New York Hospital in 1932. By reviewing the data collected on breech deliveries, we hope that some conclusions can be drawn that may direct us to better management and lead to a reduction in the fetal mortality rate of breech deliveries. In a search for more information concerning this problem, the x-ray was utilized to determine what influence the attitude of the fetus *in utero* had upon the mechanism of labor in breech deliveries.

Otto Brakemann, in 1936, reported the results of a similar radiological survey. His series was not conclusive but he gained the impression that, in breech presentation, with the vertex in a deflexed attitude, more difficulty in labor resulted. Also, he felt that such deliveries necessitated operative procedures more frequently. It was of interest to note whether the information from our x-ray files substantiated his theory, and if so, how such information could be used to better practical advantage.

### Incidence of Breech Presentation

From Sept. 1, 1932, to Dec. 31, 1947, there were 45,837 full-term and premature deliveries in the Woman's Clinic of the New York Hospital. Of this number, there were 1,918 full-term and premature breech deliveries. Our incidence of breech presentation, therefore, is 4.2 per cent, which compares very closely to other large series reported in the literature. (Heaton, Tompkins, and Martius reported an incidence of 4.6, 4.7, and 3.4 per cent, respectively) Martius, excluding all premature infants and twins, found the incidence of breech presentation to be 2.5 per cent of full-term single pregnancy deliveries. Hecker, whom Martius quotes in Halban and Seitz, found an incidence of 3.2 per cent of all births. Of the breech deliveries he studied, 74.5 per cent were frank breech presentations and 24.5 per cent full breech presentations. He also stated that one per cent of them presented with a knee.

In the Woman's Clinic of the New York Hospital, 54.93 per cent of patients with breech presentations were primiparas, 45.07 per cent multiparas. There were 91 cesarean sections done, an incidence of 4.7 per cent. This is slightly higher than the incidence of 3 to 4.5 per cent for cesarean sections in all deliveries at the Clinic.

### Etiology of Breech Presentation

There are many theories concerning the etiology of breech presentation. The principal factors that are discussed in the literature are: pelvic contractions,

stasis.<sup>31, 32</sup> Therefore, local anesthesia would be the anesthetic of choice, or an inhalation anesthetic with a high oxygen proportion.

3. Prophylactic digitalization might well be employed routinely in these patients prior to any operative procedure.

### Summary

The twenty-three reported cases of sickle cell anemia complicating pregnancy have been reviewed. Six additional cases are reported and tentative recommendations as to therapy have been made.

### Conclusions

1. Sickle cell anemia is a serious complication of pregnancy. The prognosis for both mother and child is very grave.

2. Toxemia of pregnancy, premature labor, morbidity, and mortality are definitely increased in these patients.

3. The treatment of a patient in the active phase or crisis stage is unsatisfactory. Prophylactic digitalization is indicated.

4. Treatment of the patient in the latent phase should consist of prophylactic digitalization and induction of labor as soon as viability of the fetus is established.

5. Patients with known sickle cell anemia who are not pregnant should have therapeutic sterilization or use adequate contraceptive measures.

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9 per cent; intracranial hemorrhage, 8 per cent; premature separation of the placenta and placenta previa, 5 per cent; and, in the other 9 per cent, the cause was dubiously syphilis, hemorrhagic disease, or was undetermined. But eliminating prematurity and congenital anomalies, the corrected fetal mortality is 6.0 per cent. There was no obvious difference between multiparas and primiparas when the cause of death in each group was analyzed, except for the deaths that occurred due to prolapse of the cord. Such accidents were responsible for 14 per cent of the fetal deaths in multiparas, but for only 6 per cent of the fetal deaths in primiparas. It is suggested that the multiparous patient may suddenly become fully dilated much more frequently than the primiparous patient. A prolapsed cord might be undetected in such cases until asphyxia of the fetus has occurred. The number of excessive-sized infants (4,000 Gm. or over) was statistically the same in each group. The number of premature deaths in each group revealed no significant statistical difference.

In Table I we have compared the fetal mortality rate in spontaneous deliveries with that in operative deliveries. There is a preponderance of operative deliveries. In the accumulated data of the Clinic, a breech delivery is classified as a breech extraction and thus an operative delivery if even so much as a Mauriceau-Smellie-Veit maneuver is necessary. If forceps are used on the aftercoming head, it of course is classified as an operative delivery. The mortality rate for the fetus is higher in spontaneous than in operative deliveries, 19.8 per cent and 11.5 per cent, respectively. However, premature infants are more likely to have a spontaneous delivery.

The operative deliveries have been subdivided in the manner shown in Table II. There is little difference in the fetal mortality when the breech extraction deliveries are compared with those in which the forceps were used on the aftercoming head. When cesarean section was done, the fetal mortality dropped significantly to 4 per cent. The fetal death in each cesarean section case was caused by abruptio placenta. In view of the lesser fetal risk with the employment of abdominal delivery, it has been the policy of this Clinic to do a cesarean section on most elderly primiparas at term with a breech presentation. The result has been very gratifying.

TABLE II. INFANTILE MORTALITY IN BREECH PRESENTATION BY TYPES OF OPERATIVE DELIVERY

	PRIMIPARAS			MULTIPARAS			TOTAL		
	NO. CASES	INFANT DEATHS	PER CENT	NO. CASES	INFANT DEATHS	PER CENT	NO. CASES	INFANT DEATHS	PER CENT
Breech extraction	641	63	9.9	583	88	15.1	1,224	151	12.3
Forceps on after-coming head	191	19	9.9	51	6	11.8	242	25	10.3
Cesarean section	50	2	4.0	40	2	5.0	90	4	4.4

### Maternal Mortality

In our series of 1,918 breech deliveries, six maternal deaths were noted. The maternal mortality rate in breech deliveries is 0.31 per cent, or 3.1 per thousand cases. The diagnosis in each case is: hemorrhage, 2 cases; acute yellow atrophy of the liver, 1 case; and puerperal infection with peritonitis, 3 cases.

### Radiological Survey

An attempt has been made to evaluate radiological studies of the fetus in breech presentation. Brakemann's impression that operative interference is necessary most commonly in the cases showing an extended attitude of the fetus is challenged in this study. A comparable number of cases are reported and the clinical result noted in each case.

abnormalities of the fetal head, abnormalities of the uterus, prematurity, hydramnios, and hereditary tendencies.

Pendleton Tompkins, after reviewing the causes of breech presentation, concluded that the so-called "classic" causes accounted for only 6 per cent of the cases. He does not feel that a contracted pelvis could be considered a cause, since in 89 per cent of his cases there was no evidence of contraction.

Many of the patients with breech presentation had a radiological examination of the maternal pelvis. The data obtained from these films and that obtained from clinical examinations of the pelvis revealed that in 87.1 per cent of our cases of breech presentation the pelvis were normal.

A comparable number of patients with infants presenting by vertex was studied, choosing at random the cross-section year 1943. Of 3,017 deliveries recorded, normal pelvis were encountered in 89.2 per cent. From these data it would appear that contraction of the pelvis is not an etiological factor in breech presentation.

Fetal Mortality

Martius, at the University of Bonn, found the fetal mortality in breech deliveries to be 14 per cent. Goethals, in Boston, reported in 1936 that the crude fetal mortality figures in uncomplicated breech deliveries for primiparas with a single pregnancy were 18.1 per cent; multiparas with a single pregnancy, 17.2 per cent. After macerated and badly malformed babies were excluded, the corrected mortality rate was 13.6 per cent, subdivided as follows: premature infants, 53.6 per cent mortality; immature infants, 10.0 per cent mortality. The mature babies had a 6.9 per cent fetal mortality, representing the risk in uncomplicated deliveries with a mature baby. Dieckmann reported the gross fetal mortality of term babies to be 7.7 per cent. His premature infants had a 25+ per cent fetal mortality. Causes of death were: prematurity, intracranial injury, asphyxia, and a small number of visceral lesions.

In our series (as shown in Table I) there is a total of 1,660 full-term and premature deliveries with 200 deaths. Note that the multiparas have a higher fetal mortality rate than the primiparas. The total gross fetal mortality rate is 12 per cent. The cause for the increased rate in multiparous patients is not clear. Goethals found that mature babies of multiparous patients suffered a greater risk than those of primiparas. He investigated the possibility that multiparas are more likely to give birth to large and overdeveloped infants. However, in his series, it was found that the fetal mortality rate was lower in the large (8 pounds plus) babies of multiparas compared with the large one of primiparas. There was a higher percentage of large babies in multiparas in the series reported by Goethals.

TABLE I. INFANTILE MORTALITY IN BREECH PRESENTATION

	SPONTANEOUS DELIVERIES			OPERATIVE DELIVERIES			TOTAL		
	NO. CASES	INFANT DEATHS	PER CENT	NO. CASES	INFANT DEATHS	PER CENT	NO. CASES	INFANT DEATHS	PER CENT
Primiparas	29	5	17.2	883	84	9.5	912	89	9.8
Multiparas	72	15	20.8	676	96	14.2	748	111	14.8
Grand total	101	20	19.8	1,559	180	11.5	1,660	200	12.0

The cause of fetal death was checked in our 200 cases and the etiological factors rank in the following order: Prematurity, 31 per cent; congenital anomalies, 19 per cent; intrauterine asphyxia incident to delivery, 10 per cent; prolapsed cord or cord tight about the neck, 9 per cent; intrauterine infection,



radiological survey; 160 of these delivered vaginally, and 28 by means of cesarean section. The remaining cases were not considered suitable for analysis. In Table VI, the duration of labor in the 160 vaginal breech deliveries is tabulated. The data are most favorable in the 80 cases which had an extended (neutral or military) attitude of the vertex in utero. In this group, 73.8 per cent had labors lasting eighteen hours or less. Since it is taught that the duration of labor in all deliveries of primiparas is normally eighteen hours (twelve hours in multiparas), it would seem logical to compare the duration of labor in breech deliveries to this eighteen-hour figure. The median duration of labor in the flexed, extended, and hyperextended heads was seventeen, thirteen, and eighteen hours, respectively. In our data for the 1,660 full-term and premature breech deliveries, the median duration of labor was found to be eleven hours. In 1943 (a cross-section year chosen at random), there were 3,116 deliveries with the fetus presenting by the vertex, and the median duration of labor in this group was found to be ten hours. We realize that the small series of 160 cases is hardly comparable to 1,660 cases.

TABLE VI. BREECH DELIVERIES. DURATION OF LABOR IN VAGINAL DELIVERIES

HOURS OF LABOR	ATTITUDE OF VERTEX						TOTAL	
	FLEXED		EXTENDED		HYPEREXTENDED			
	CASES	PER CENT	CASES	PER CENT	CASES	PER CENT	CASES	PER CENT
1-18	36	59.0	59	73.8	10	52.6	105	65.6
19-35	15	24.6	12	15.0	6	31.6	33	20.6
36-50	7	11.5	3	3.7	1	5.3	11	6.9
50 plus	3	4.9	6	7.5	2	10.5	11	6.9
Total	61	100.0	80	100.0	19	100.0	160	100.0

In order to learn more about the mechanism of labor, many of our films were taken after the onset of labor. Some were rechecked in the first stage and others were checked in the second stage of labor. Two were taken with the breech on the perineum. Fig. 1 is just such an example. It is to be noted that the vertex is *neutrally* placed and the spine is fairly straight with some slight degree of flexion in it. The arms are in front and flexed. This case resulted in a very easy assisted breech delivery. The neutral status of the vertex is most commonly encountered, and it is here demonstrated that the neutral status of the vertex is maintained in the second stage of labor just prior to engagement of the aftercoming head in the pelvis.

In comparison, we have an x-ray (Fig. 2) showing the fetus with marked *hyperextension* of the vertex and spine. Note that the face of the fetus is looking up and there is a sharp angulation of the neck; the remaining portion of the spine is straight but not hyperextended. It would appear that the fetus needed more room in utero. The maternal pelvis in this case was normal. Due to prolapse of the cord at full dilatation of the cervix, a breech extraction was done and Piper forceps applied to the aftercoming head. The vertex was delivered in the occiput anterior position. The infant showed signs of asphyxia, but responded favorably to resuscitation efforts. There was a tendency for the head to return to its fetal attitude after delivery. A cephalhematoma and some flaccidity of the lower extremities were noted. Early improvement occurred, but one month later it was apparent there was a transection of the cord at the level of T-1. Upon looking at the hyperextended attitude of the breech in utero it is possible that the lesion in the cord occurred as a result of pressure in utero.

In Fig. 3 another case is demonstrated with a marked degree of hyperextension. The present film was taken in the last week of pregnancy prior to the onset of labor. Again, the sharp angulation of the cervical portion of the

Brakemann (Table III) did not indicate the exact data concerning the course of labor and delivery in his cases. He merely stated that a more difficult labor and delivery was noted in those having a deflexed attitude of the vertex.

TABLE III. RADIOLOGICAL SURVEY OF FETAL ATTITUDE IN BREECH PRESENTATION  
(From Brakemann, Otto: *Ztschr. f. Geburtsh u. Gynäk.* 112: 154, 1936.  
191 Cases of X-ray Examination With Fetus in Utero)

ATTITUDE OF VERTEX	NUMBER CASES	PER CENT
Complete flexion	42	21.9
Neutral (middle)	116	60.7
Mild extension (sinciput)	12	6.2
Forehead extension	19	9.9
Face extension	2	1.0
Total	191	99.7

In the data collected at the Woman's Clinic of the New York Hospital (Table IV) 216 cases were reviewed. In all of these, an abdominal flat plate was made and in many a pelvic radiological examination. Again, as shown in the data of Brakemann, the deflexed, neutral, or military attitude was most frequently encountered. In all cases that had deflexion of the vertex beyond the neutral or military attitude, the term hyperextension is used. Emphasis should be placed, we think, on the fact that the most common attitude for the head to assume is that of neutral or the so-called "military." The comparable figures in this series and that of Brakemann would seem to be statistically correct.

TABLE IV. RADIOLOGICAL SURVEY OF FETAL ATTITUDE IN BREECH PRESENTATION

ATTITUDE OF VERTEX	NO. CASES	PER CENT
Complete flexion	86	39.8
Neutral extension (Middle, military)	107	49.5
Hyperextension (Sinciput, forehead, face)	23	10.7
Total	216	100.0

In the mechanism of labor of breeches, the important feature of the fetal attitude is that of the relationship of the vertex to the spine. It is postulated that the forces of labor are exerted by the fundus of the uterus upon the vertex and transmitted through the fetal spine to the presenting part. Such an action causes descent and engagement of the breech. Another factor in causing descent is the straightening out of the spine and body of the fetus. Thus it would seem that the neutral or military attitude of the vertex and spine would be the most favorable. The data concerning the relationship of the vertex to the spine are tabulated in Table V. The interpretation of the degree of deflexion of the spine is subject to a certain amount of error due to individual interpretation of the films. Only in the cases with *hyperextension of the vertex* did one see *hyperextension of the spine*.

TABLE V. RELATIONSHIP OF VERTEX TO SPINE OF FETUS IN BREECH PRESENTATION

ATTITUDE OF VERTEX	NUMBER CASES	ATTITUDE OF SPINE		
		FLEXED	EXTENDED	HYPEREXTENDED
Flexed	86	85	1	0
Extended	107	96	11	0
Hyperextended	23	1	11	11
Total	216	182	23	11

It is commonly taught that the duration of labor with breech presentations is prolonged. This problem was investigated in the 216 cases subjected to the

approach. In Table VII the results in twenty-three cases of hyperextension of the vertex are summarized. Not all of these cases were deflexed as much as the two demonstrated cases. They all, however, were extended beyond the neutral or military attitude. In the data presented in this brief summary, it is seen that four patients were delivered by cesarean section. Two of these had contracted pelvises, and in one the diagnosis of placenta previa was made. The fourth

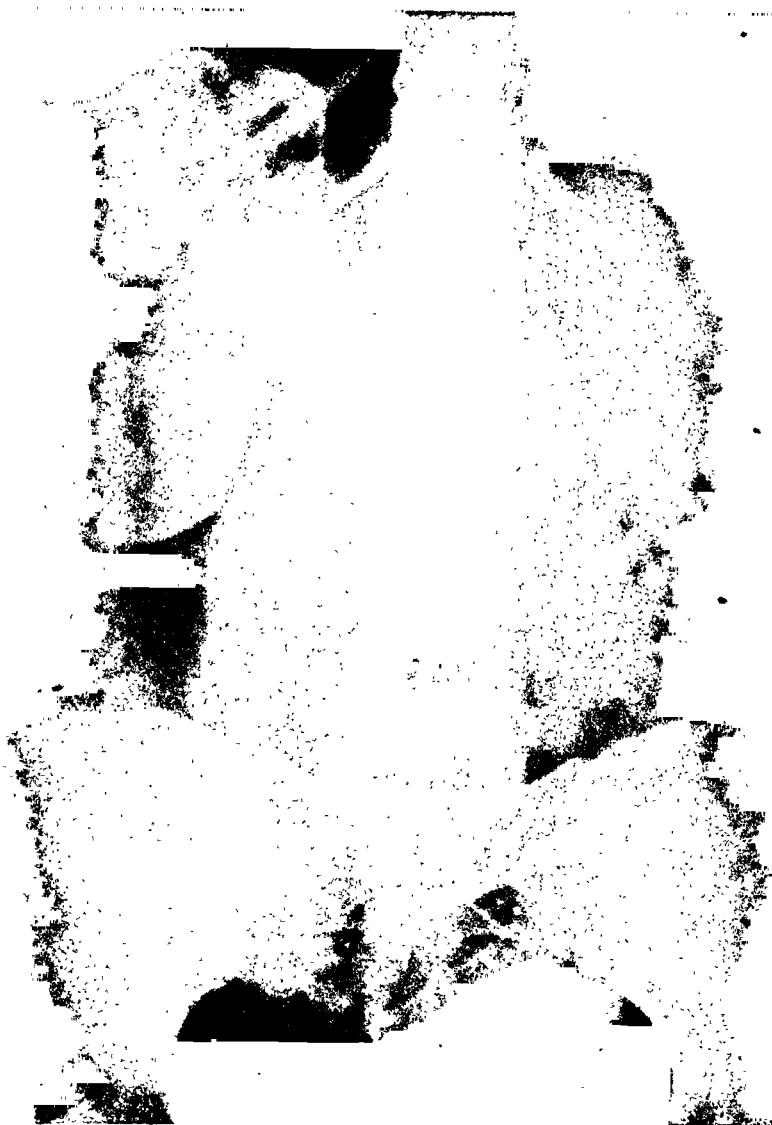


Fig. 2.

had an abdominal delivery; no other feature complicated the clinical course except that no progress was made during twenty-four hours of labor. Incidentally, a repeat x-ray taken at the end of the twenty-four hours of labor showed no change in the fetal attitude. The incidence of cesarean section in this very small group of twenty-three cases is 17.4 per cent, considerably higher than that of cesarean section in all breech deliveries in this Clinic, which was previously quoted as 4.7 per cent.

Three of the cases with hyperextension had the frank breech decomposed or "broken up." We might add that we do not do such procedures in the Woman's Clinic unless the progress of the breech is arrested.

spine is to be noted. The face is looking upward; the thoracic portion of the spine is also hyperextended. The arms are in front of the fetus with the forearms hanging downward. After eleven hours of early labor, the patient came to the Clinic and examination revealed the cervix to be 4 cm. dilated. There was a single footling breech presentation. The fetal attitude was rechecked by x-ray and no change had taken place. Because the patient had a contracted pelvis (anthropoid configuration with a narrow transverse diameter of the inlet), a low-flap cesarean section was done. An apparently normal infant weighing 2,940 Gm. was born. Incidentally, a nuchal hitch was encountered when extracting the fetus through the uterine incision. The poor flexion of the arms undoubtedly predisposes to the occurrence of nuchal hitches.



Fig. 1.

These last two cases represent our most extreme cases of deflexed attitudes, and the management of such cases would seem to demand especial attention. Vaginal and abdominal deliveries were accomplished in the two cases, respectively. Because the result with vaginal delivery was unfortunate in the first case, we do not feel that all such cases should have a cesarean section per se. Individualization of each patient with such a problem would seem to be the best

should be visualized also to learn the configuration and the measurements. By such adjuncts, more information may be obtained about the mechanism of labor for the breech, the shoulders, and the aftercoming head.

TABLE VII. CLINICAL RESULTS OF BREECH DELIVERIES WITH HYPEREXTENSION OF VERTEX IN UTERO

CASE	HOURS OF LABOR	SPINE, ATTITUDE	TYPE OF DELIVERY	PARITY OF MOTHER	CONDITION OF INFANT
1	None	Extended	Low flap cesarean section (placenta previa)	P	Good
2	None	Extended	Classical cesarean section (contracted pelvis)	P	Good
3	5	Extended	Frank breech extraction	M	Good (4,600 Gm.)
4	5	Hyperextended	Frank breech extraction	P	Good
5	5	Hyperextended	Forceps on aftercoming head and frank breech extraction	P	Good
6	8	Extended	Frank breech extraction	P	Good
7	9	Extended	Frank breech extraction	P	Good
8	13	Hyperextended	Single footling breech extrac- tion and forceps on after- coming head	P	Good
9	14	Hyperextended	Double footling breech extrac- tion and forceps on after- coming head	P	Good, but congen- ital anomaly of neck
10	15	Hyperextended	Low-flap cesarean section (contracted pelvis)	P	Good
11	16	Flexed	Frank breech extraction and forceps on aftercoming head	P	Good
12	16	Hyperextended	Spontaneous breech delivery	P	Good
13	18	Hyperextended	Spontaneous breech delivery	M	Good
14	20	Hyperextended	Frank breech delivery	P	Good
15	23	Hyperextended	Double footling breech ex- traction	P	Good
16	24	Hyperextended	Low-flap cesarean section	P	Good
17	25	Hyperextended	Single footling breech extrac- tion and forceps on after- coming head (prolapsed cord)	P	Asplasia Paralysis
18	25	Extended	Decomposition; frank breech extraction	P	Good
19	26	Extended	Decomposition; frank breech extraction	P	Good
20	28	Extended	Frank breech extraction	P	Good
21	49	Extended	Frank breech extraction	P	Good
22	64	Extended	Frank breech extraction	P	Good
23	67	Extended	Decomposition; frank breech extraction	P	Deadborn
Median Duration of Labor: Hyperextended head (excluding Nos. 1, 2, 10, 16)					18 hours
Total breech deliveries					11 hours
Vertex presentations					10 hours

### Summary and Conclusions

At the Woman's Clinic of the New York Hospital, a study has been made of the full-term and premature deliveries in breech presentation. Emphasis has been placed on the attitude of the fetus as shown by radiological studies. Brake-mann drew attention to the problem of the deflexed head in 1936.

The data of our breech deliveries have been tabulated. One thousand nine hundred eighteen breech deliveries occurred in 45,837 full-term and premature

One infant was lost in the process of delivery. Therefore, the fetal mortality is 4.3 per cent in cases with hyperextension of the vertex. In the instance cited, there was a prolonged labor and a resistant cervix. This death might have been prevented by the employment of a cesarean section at the proper time. In only one instance was there found a congenital anomaly (cyst) of the neck that might explain the hyperextension of the vertex.



Fig. 3.

The median duration of labor in this group with hyperextension of the vertex is eighteen hours. However, the four who had abdominal deliveries were excluded from these figures. The two patients who had labor prior to their sections obviously were destined to have a period of labor considerably longer than eighteen hours.

It is our opinion that the series of cases with hyperextended heads is too small to be statistically sound. However, more operative interference was done in the group of cases with the hyperextended attitude. The duration of labor is no longer for vaginal deliveries (shown in Table VII) than is that of the average primipara in all deliveries.

The x-ray should be utilized when possible in the study of such cases. A flat plate of the abdomen and a lateral may be necessary to evaluate properly the deflexion and in many cases the rotation of the head. The maternal pelvis

## TUBAL STERILIZATION THROUGH THE VAGINA\*

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IT IS not the purpose of this paper to discuss the moral or ethical problem of sterilization. This is a question which must be decided by the patient, her husband, and the consulting physician. Certainly, the religious beliefs of both the patient and physician should be respected; however, it is our opinion that a married couple has the right to determine the size of their family whether this be accomplished by total abstinence, contraceptives, or sterilization.

In a review of the literature and present-day textbooks, one is impressed by the variety of techniques still advocated for sterilization notwithstanding that there have been fewer failures reported following the Pomeroy technique. Pregnancies continue to be reported after the performance of preventive operations regardless of the technique that has been used. Many additional reports in the literature indicate that pregnancy can occur even after removal of a major portion of the uterus. This further substantiates the statement that hysterectomy with bilateral salpingo-oophorectomy is the only positive safeguard. Until the perfect operation is devised, we are confronted, therefore, with the problem of choosing the safest, most appropriate, and most effective method of sterilization in that large group of women in whom such a mutilating operation should not be considered.

In an extensive résumé of the literature Knight,<sup>1</sup> in 1946, compared the results obtained with the Pomeroy, the Madlener, and resection of the cornu methods of sterilization. He concluded that the Pomeroy is the safest, simplest, and the most easily performed method, that it produces 50 per cent better results than the Madlener technique, and that the cornual resection technique is least efficient. The reports of Lull<sup>2</sup> and ~~Thornton~~<sup>3</sup> in 1,031 patients with no failures substantiate these conclusions. It should be pointed out that a majority of the sterilizations reported in the literature were done on the pregnant or puerperal uterus. We should like to suggest that the conditions and changes resulting from pregnancy may be a factor in many of the failures and that failure is not entirely due to the technique used. However, Lull's results in 812 cases suggest that this conclusion may not be valid. Four of the five deaths reported in this series, however, followed operations on the pregnant or puerperal uterus and we believe that this lends weight to the conclusions which we shall discuss later in this paper.

It has long been our feeling that sterilization at the time of therapeutic abortion is an unsatisfactory and at times dangerous procedure. I have witnessed the death of a young married woman upon whom a therapeutic abortion and sterilization had been performed for rheumatic heart disease. She developed a pelvic cellulitis and her damaged heart could not resist the added load of the infection.

\*Presented before a meeting of the Chicago Gynecological Society, May 21, 1948.

deliveries. The incidence of breech presentation is 4.2 per cent. The fetal mortality rate in breech deliveries is 14.8 per cent for multiparas and 9.8 per cent for primiparas, a total gross fetal mortality rate of 12 per cent. The corrected fetal mortality rate is 6 per cent if premature infants and congenital anomalies are eliminated.

Prematurity, congenital anomalies, intrauterine asphxia, prolapsed cord or cord tight about the neck, intrauterine infection, intracranial hemorrhage, and premature separation of the placenta are the major causes of fetal death in our breech deliveries. The only significant difference noted in the fetal deaths of multiparas and primiparas was that prolapse of the cord and cord tight about the neck occurred in multiparous patients more than twice as often as in primiparous patients.

Cesarean section carries with it a lower fetal mortality rate in breech deliveries, 4.4 per cent, which is about one-half that of other types of operative deliveries.

Maternal mortality in breech deliveries is 0.31 per cent.

The neutral or military attitude of the vertex is most commonly encountered in breech presentation. The duration of labor with the vertex in the neutral attitude is shorter than in those with the vertex flexed or hyperextended.

The theory that extreme hyperextension of the vertex may be responsible for longer labor is not proved by this small series of cases. The incidence of cesarean section was more than four times as high in the cases with extreme hyperextension of the vertex as in all deliveries of the Clinic. The fetal mortality in the summarized cases of extreme hyperextension is 4.3 per cent. We do not believe cesarean section is indicated because of a hyperextended vertex per se. Individualization of such cases must be stressed. The study of the mechanism of labor in each case by means of the x-ray will aid in the management of the hyperextended breech presentation.

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We believe that laparotomy for sterilization alone is an entirely unjustifiable procedure, except perhaps postpartum sterilization in selected cases, as suggested by Adair and Brown<sup>6</sup> before this Society in 1939. We do not do as many postpartum sterilizations as are done in other hospitals, ours being limited to those patients having very little outlet relaxation and in some patients who have been unable to use contraceptives successfully, thereby presenting an economic and social problem. We believe that most patients who have had several vaginal deliveries, in whom sterilization is indicated, have in addition so much outlet relaxation that vaginal plastic surgery is also generally indicated. In such cases, we prefer that the patients return at a later and safer date for sterilization and plastic repair. It has been our experience that the ideal time for this procedure is approximately four to six months post partum. Involution is by no means complete in six weeks as stated in the standard textbooks on obstetrics. We believe that the operative risk is lessened and the chances of failure of the tubal sterilization are decreased in direct ratio to the stage of involution. Nearly all of the complications encountered have occurred in patients who have been sterilized at the time of therapeutic abortion or on incompletely involuted uteri. These complications have not been critical, but when superimposed upon such conditions as severe heart, kidney, or pulmonary disease they may be a deciding factor in the patient's recovery.

In most of these reports no mention is made of mortality except the five deaths reported by Lull in his series of 589 sterilizations by the Pomeroy technique. Four of these five deaths were in women who were pregnant at the time of sterilization. The other woman died following a vaginal plastic and sterilization and Lull explains that the sterilization had no bearing on the outcome. Of the four pregnant women, one died following cesarean section and sterilization and death resulted from the primary indication for surgery. Three had hysterotomies and sterilization and we assume that these were done by laparotomy. We feel that had these uteri been emptied vaginally and the sterilizations been postponed until involution was complete, the end results would have been more successful. However, if these hysterotomies and sterilizations were performed per vaginam, the additional technical difficulties due to an enlarged vascular uterus, increased operative time, and prolonged anesthesia with the resultant bleeding and trauma, all superimposed upon a poor operative risk, probably may have been sufficient to influence the fatal outcomes.

Due to the impetus given by Dr. N. Sproat Heaney in the field of vaginal surgery, all at Presbyterian Hospital are convinced that when it becomes necessary to empty the pregnant uterus (even up to the period of viability), it is much safer to do so vaginally rather than by the abdominal route. Moreover, we feel just as strongly that sterilization should not be done at the time of vaginal hysterotomy except in rare instances.

This paper covers a series of 169 patients on whom sterilization was done on the nonpregnant uterus. The age distribution is indicated in Table I.

The indications for sterilization are shown in Table II.

This report includes sterilizations done at the time of therapeutic abortion but not those performed at the time of cesarean section. Undoubtedly, the number would be much larger were it not for the fact that we have performed vaginal hysterectomy as the means of sterilization in many cases, particularly in older women because of co-existing pelvic pathology, such as prolapsus uteri, badly lacerated cervixes, small fibroids, uncontrollable menorrhagia, or severe dysmenorrhea. Early in this series most of the sterilizations were accomplished by the cornual resection of the tubes but more recently most of us have used the original Pomeroy technique or a slight modification of it, exclusively. We routinely label the resected portions of the tubes, left and right, and send them to the pathologic laboratory for histologic verification that we have resected a portion of the tube in its entirety. This procedure is particularly important if one insists on doing a sterilization in conjunction with therapeutic abortion, as the tubes are more difficult to identify in the presence of an enlarged uterus and their recognition may not be easy because of the associated hyperemia and edema. Some of the failures reported following attempted sterilizations might have been due to the resection of a portion of the round ligaments instead of the tubes. It is important that the entire tube be visualized and traced out to its fimbriated end. This is especially so when the operation is performed per vaginam or through a small abdominal incision immediately following delivery. The raw stumps must be carefully inspected for bleeding before dropping them back in the pelvis.

As far as we are able to determine we have had only one failure with either Pomeroy or cornual resection technique when performed on the non-pregnant uterus. Perhaps others have had the opportunity of seeing some of our failures. As we shall point out later, sterilization done at the time of therapeutic abortion has not been as successful when the cornual resection technique has been employed. In recent years we have abandoned the routine testing of the patency of the tubes ten to twelve weeks following the operation, feeling that patency might be re-established by this procedure. It is well known that tubal epithelium possesses unusual ability to regenerate after injury, whether it be traumatic or inflammatory in origin.

Dippel,<sup>4</sup> in 1940, in a critical analysis of five failures of the Madlener technique was able, at subsequent laparotomy, to demonstrate by serial sections of the operation sites that failures were due to tuboperitoneal fistula or canalization of the damaged lumina. One can easily visualize how the instillation of any opaque medium or air might re-establish tubal patency in some cases.

Dieckmann and Hauser,<sup>5</sup> in a report of failures of tubal sterilization using the Madlener technique, had the highest percentage of failures in their twenty-four-hour post partum cases. They point out that the alterations of the tubes in association with pregnancy may be factors in these failures. With this we concur. We cannot agree with their statement that their failures when using the vaginal technique should be due to difficulty in exposing the tubes unless they were operating on the pregnant uterus.

There were no deaths in the series. There were 52 cases of sterilization without plastic. There was a morbidity of two days in three cases. There were 117 cases of sterilization and additional procedures, with morbidity in 31 cases, an average of 4.9 days (Table VI).

TABLE VI. Morbidity

Sterilization without plastic	52 cases
Cases of morbidity	3 (2 days)
Sterilization and additional procedures	117 cases
Cases of morbidity	31 (average 4.9 days)

The etiology of the morbidity is indicated in Table VII.

TABLE VII

Pelvic cellulitis	15
Cystitis	8
Bladder injury	1
Pelvic abscess	2
Postoperative bleeding	2
Pneumonia	1

There was only one failure in the vaginal sterilization on the nonpregnant uterus, a percentage of 0.59 per cent. The technique employed was cornual resection (Table VIII).

TABLE VIII

Vaginal sterilization on nonpregnant uterus	169 cases
Failures (cornual resection)	1 or 0.59 per cent

A ten-year survey of vaginal sterilization with therapeutic abortion shows the following results:

TABLE IX

TECHNIQUE		SUCCESSFUL		FAILURES	
		NO.	PER CENT	NO.	PER CENT
Pomeroy	19	18	94.8	1	5.2
Cornual resection	11	7	63.6	4	36.4
Total	30	25	83.4	5	16.6

Six of the thirty patients were morbid for an average of five days. The average hospital stay was ten days with no additional surgical procedures having been done.

### Conclusions

We have reported the sterilization of 169 nonpregnant patients with one failure. The morbidity was almost nil when no additional surgical procedures were done. The morbidity and hospital stay were markedly increased with the addition of plastic procedures.

Our results with the combination of therapeutic abortion and sterilization have been much less favorable; one failure in nineteen when the Pomeroy technique was carried out and four failures out of eleven when cornual resection was employed. The hospital stay was increased in spite of the fact that no additional plastic work was done. Although there were no deaths following any of the procedures, two patients were critically ill following therapeutic abortion and sterilization.

TABLE I. NONPREGNANT AGE GROUP

18 to 19 years	4
20 to 29 years	51
30 to 39 years	106
40 and over	8
	169

TABLE II. INDICATIONS FOR STERILIZATION

Pelvic pathology	105
Neurological	24
Cardiac disease	15
Kidney disease	9
Pulmonary tuberculosis	5
Sociological	5
Diabetes	4
Repeated fetal malformations	1
Ulcerative colitis	1
	169

In this series of 169 cases there were associated physical complications as indicated in Table III.

TABLE III. ASSOCIATED PHYSICAL COMPLICATIONS

Rectocele	104
Cystocele	68
Urethrocele	35
Lacerated cervix	13
Prolapse of uterus	5
Vesicovaginal fistula	1
Third degree tear	2

In addition to sterilization other operative procedures were performed on these 169 patients as shown in Table IV.

TABLE IV. ADDITIONAL OPERATIVE PROCEDURES

Dilatation and curettage	169
Perineorrhaphy	104
Anterior repair	68
Urethroplastic	35
Amputation of cervix	15
Vaginal round ligament shortening	14
Miscellaneous	4

The technique of sterilization and the hospital stay are indicated in Table V.

TABLE V. TECHNIQUE OF STERILIZATION

Pomeroy, posterior colpotomy	64	} 62.7 per cent
Pomeroy, anterior colpotomy	42	
Cornual resection, anterior colpotomy	35	} 34.9 per cent
Cornual resection, posterior colpotomy	25	
Defundectomy, anterior colpotomy	3	2.4 per cent
HOSPITAL STAY		
Pomeroy (without plastic)		6.4 days
Cornual resection (without plastic)		10.2 days
Sterilization and vaginal plastic		11.0 days

Earlier, if the uterus lay anterior, we would do the tubal operation through an anterior colpotomy, especially if an anterior colporrhaphy were also to be done, while if the uterus were retroverted the work would be carried out through a posterior incision. Dr. Boyesen indicated in one table the number of operations performed by each approach. He did not show which route yielded the higher morbidity. When a posterior colpotomy is done and the incision is closed by interrupted sutures, if an abscess forms in the cul-de-sac, the sutures will soon give way and the abscess will drain spontaneously, while, if an anterior colpotomy is used, then puncture of the abscess usually becomes necessary and convalescence is delayed. For this reason I always use the posterior approach, rarely have I had to desert this route and do the work anteriorly. The advantages of the vaginal attack over a laparotomy for sterilization are the same as exist between vaginal and abdominal operations generally and need no especial elucidation. I have never done a plain sterilization by the abdominal route.

Though the wishes of the patient must be taken into consideration when a therapeutic abortion or sterilization is to be performed, the physician must assume the full responsibility for the decision and, after the operation is completed, he must impress the patient with the idea that her desires were in no way responsible for his decision. Instead he should unequivocally state that the operation was absolutely necessary. This will protect the patient from psychic trauma and prevent her from deciding at some future date that she had been too hasty in her decision and that another pregnancy is necessary for her happiness. No woman can be more miserable than a patient who has changed her mind regarding the desirability of pregnancy after she has already been "successfully" operated upon.

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## Discussion

DR. JOHN I. BREWER.—When sterilization procedures are under consideration, the consulting physician must consider several things before making recommendations. If the sterilization is desired simply because the family is large enough, and if there are no pelvic lesions in the wife that demand surgery, the physician should advise that the husband's vas should be ligated. This is simple, easy of accomplishment, entails no risk, and is preferable to entering the peritoneal cavity of the woman. If there are indications for pelvic surgery in the woman, sterilization may be carried out as a part of that procedure. The author believes that sterilization of the female is best accomplished by ligation of the oviducts vaginally. In most instances this can be accomplished. There are a few exceptions. Tubal ligation or cornual resection procedures are performed abdominally when there is some existing pathology that requires an abdominal approach. If an abdominal hysterotomy or elective cesarean section is indicated, I do not believe that tubal ligation increases morbidity or mortality. From the author's experience and belief, vaginal hysterotomy for termination of a pregnancy is accompanied by increased morbidity and mortality if vaginal ligation of the tubes is carried out as a part of the same procedure. This is quite possible and his reasoning is sound. We shall limit our procedures accordingly in the future. The figures reveal that sterilization procedures are more satisfactorily performed when the patient is not pregnant. The reasons for the failures are not explained. It is apparently a fact, however, that the results are not as good. This and the difficulties encountered when sterilization procedures accompany vaginal hysterotomies confirm a principle that some of us are teaching. This is that surgical procedures should be avoided during pregnancy if at all possible. When surgery must be done it should be limited to the bare minimum. We are in hearty accord with the author's statement that sterilization in most instances is best accomplished several months after the pregnancy is terminated and that the vaginal route is the one of choice. Performance of the procedure through the posterior cul-de-sac is preferable.

We agree that the abdomen should not be opened through an abdominal incision for the purpose of sterilization alone. Postpartum sterilization is rarely indicated. It is, however, a much better procedure than one which was previously performed, namely, a cesarean the only indication for which was a desire to ligate the tubes.

DR. N. SPROAT HEANEY, Beverly Hills, Calif.—I have been greatly interested in advancing the attack on pelvic conditions by the vaginal approach, including sterilization per vaginam. No one who has mastered the technique of vaginal surgery would any more think of entering the abdomen to perform a therapeutic abortion, pure and simple, than an otolaryngologist would think of draining the antrum of Highmore by an incision through the cheek. Because one is not acquainted with some indicated technique is no excuse for him to substitute some more dangerous operation. Vaginal sterilization has been done for years and it is a less intricate operation. One can almost always get perfectly adequate exposure of the tubes through a colpotomy incision.

When an abdominal therapeutic abortion with a sterilization is proposed, it might be well to stop and consider the indications for the operation. If a patient can stand the hazards of an operation of such potentialities, she may well, under most conditions, be allowed to go to term and normal delivery.

It has been demonstrated that pregnandiol, a biologically inert steroid similar to progesterone in chemical structure, appears in the urine coincident with the period of activity of the corpus luteum in the normal menstrual cycle and in pregnancy.<sup>13-14</sup> When progesterone is administered to normal men or women, pregnandiol excretion follows.<sup>16-17</sup> From these considerations, it has been generally accepted that progesterone, in the course of its metabolism, is changed to pregnandiol. The site of inactivation is probably in the liver.<sup>18</sup> Pregnanndiol is then excreted in the urine. Since the determination of progesterone is difficult, measurement of pregnandiol excretion in the urine has served as an index of progesterone secretion.<sup>16</sup>

Browne, Henry, and Venning were the first to study the excretion of pregnandiol in the urine in cases of threatened abortion.<sup>19</sup> They observed that the majority of patients with symptoms of threatened abortion excreting less than normal amounts of pregnandiol failed to retain the pregnancy. On the other hand, when pregnandiol excretion values remained normal, the symptoms of threatened abortion subsided and the pregnancy resumed a normal course.

Using a rapid, simple procedure for the measurement of pregnandiol in the urine (as a matter of fact, within four hours of obtaining the specimen) our laboratory has studied the variations of pregnandiol excretion in threatened abortion.<sup>20, 21</sup> These observations confirmed those of Browne, Henry, and Venning and others.<sup>22, 23</sup> Furthermore, since excretion values could be determined at frequent intervals, daily if necessary, it was possible to establish the trend of the pregnandiol levels in the urine within forty-eight to seventy-two hours. The data indicated that when such values in instances of threatened abortion remained normal or rose to normal levels from initially low values, the pregnancy was usually retained. Abortion, with rare exceptions, occurred in those cases in which the pregnandiol excretion was persistently lower than normal or fell to low values from previously normal levels. The consistency of these results led to our using the trend in pregnandiol excretion in the urine as a criterion in predicting the fate of threatened abortion. Reports from this and other laboratories indicate that the accuracy of this interpretation of the trend in pregnandiol excretion levels is close to 90 per cent.<sup>21, 24, 25</sup>

The present report is concerned with an evaluation of progesterone therapy in 335 cases of threatened abortion in which urinary pregnandiol studies were carried out. In addition we will discuss the use of progesterone in a special group of nine patients with threatened abortion whose pregnandiol excretions were low, indicating that the prognosis for maintenance of pregnancy was poor.

### Materials and Methods

Urine specimens from a group of women with signs and symptoms of threatened abortion were submitted to this laboratory for pregnandiol estimation by the various members of the staff of Michael Reese Hospital. Wherever possible, daily samples were tested. Determinations were made according to the method previously described, on first morning, 12-hour or 24-hour specimens.<sup>26</sup> An excretion of 5 mg. in 24 hours represents the minimal normal value in early pregnancy. A tentative prognosis was made in the laboratory on the basis of repeated determinations indicating the trend of the excretion level.

## OBSERVATIONS ON THE USE OF PROGESTERONE IN THREATENED ABORTION

With Special Reference to Pregnandiol Excretion as a Guide to Therapy\*†

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THE rationale for the use of progesterone in the treatment of threatened abortion lies in the observation that this corpus luteum hormone is necessary for the maintenance of early pregnancy in experimental animals.<sup>1, 2, 3</sup> Such treatment has been given with the purpose of substituting for a deficiency in progesterone which has presumably led to the symptoms of cramps and bleeding. However, because no deficiency has been demonstrated in the reported cases, it has been impossible to assess objectively the value of this hormone in the therapy of threatened abortion. The various clinical reports show no unanimity of opinion as to dosage or mode and duration of progesterone administration, although, in general, they conclude that this hormone has a beneficial therapeutic effect.<sup>4-9</sup> Despite the widespread use of progesterone in larger doses, there has been no reported significant decrease in the incidence of unintentional abortion. Since nonendocrine factors play a large role in the etiology of threatened abortion,‡ it would seem advisable to demonstrate progesterone deficiency before this therapy is rationally employed and evaluated.

Recent advances in the knowledge of endocrine factors in reproduction indicate that practical methods are available for determining the secretory activity of the corpus luteum and the placenta.<sup>11-15</sup> In the normal menstrual cycle, the formation of the corpus luteum and elaboration of progesterone follow ovulation. After a period of ten to twelve days, regression occurs and menstruation ensues. On the other hand, when the ovum is fertilized, corpus luteum function persists throughout the first trimester of the normal pregnancy, so that production of progesterone is maintained. As function of the corpus luteum decreases toward the end of the first trimester of pregnancy, the placenta takes over the role of secreting this hormone in increasing amounts until shortly before parturition.<sup>13</sup> Thus, in normal pregnancy, the secretion of progesterone proceeds uninterruptedly.

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‡Hertig and Livingston, in studying a series of 1,000 unintentional abortions, observed that 38 per cent were due to a maternal nonendocrine factor.<sup>10</sup>



TABLE II. ANALYSIS OF CURRENT PROGESTERONE TREATMENT OF THREATENED ABORTION

PREGNANDIOL EXCRETION	TREATMENT	NO. OF CASES	CLINICAL RESULTS			
			RETENTION		ABORTION	
			NO.	PER CENT	NO.	PER CENT
Normal	Without progesterone	104	80	77	24	23
	With progesterone	87	71	82	16	18
	Total	191	151	79	40	21
Decreased	Without progesterone	106	3	3	103	97
	With progesterone	38	1	3	37	97
	Total	144	4	3	140	97

### Comments

These observations raise a serious question as to the value of currently employed dosages of progesterone in threatened abortion, and possibly as to whether it has any value at all. It has been pointed out that the rationale for the use of progesterone in threatened abortion is in part based on the demonstration that this hormone is necessary for the maintenance of pregnancy in ovariectomized animals. It would appear, therefore, that the substantiation of a deficiency in the secretion of progesterone should form one of the criteria for the treatment of this clinical state with this hormone. In view of the technical difficulty of the estimation of progesterone itself, urinary pregnandiol determinations have been employed in this study to serve as an index of progesterone secretion.

Of the 335 patients reported in this series, 191 (57 per cent) excreted normal amounts of pregnandiol and thereby demonstrated an adequate normal secretion of progesterone. Since there is no deficiency in these cases, one would not expect progesterone therapy to influence the clinical course. This concept is borne out by the fact that approximately 80 per cent of these patients, whether treated or untreated, did not abort. In view of the apparently normal endocrine relationships in these cases, at least with respect to progesterone, one must look to other reasons for the occurrence of the forty abortions. In this study, we have not examined the specimens for ovular defects. Since general and local organic disturbances were apparently eliminated as etiological agents, we have no adequate explanation at the present time except to state that these abortions were probably nonendocrine in origin.

One hundred and forty-four of the patients (43 per cent) excreted less than normal amounts of pregnandiol. These women demonstrated a deficiency in the secretion of progesterone (i.e., pregnandiol excretion of less than 5 mg. in 24 hours). Consequently we might assume that in these cases, progesterone therapy should favorably influence the course of the pregnancy. However, of the 38 women in this group who were so treated, 37 (97 per cent) aborted. Similarly, 97 per cent of the 106 untreated women lost the pregnancy. The abortion incidence in this group remained at 97 per cent whether or not treatment with progesterone was instituted.

Attempts to explain the failure of current progesterone therapy in these patients have led to the following questions:

(1) Were the amounts of progesterone employed adequate to replace the apparent deficiency in secretion by the patient?

(2) Does the persistence of decreased pregnandiol levels in the urine indicate that therapy is being given for a pregnancy which is no longer alive?

The question of adequacy may be answered by the following considerations. In this discussion, we have utilized pregnandiol excretion as an index

Information regarding the onset of symptoms of threatened abortion with relationship to the duration of pregnancy, type of therapy, and clinical course was subsequently obtained in approximately 90 per cent of the cases from the physicians participating in this study.

This report is concerned with the findings only in those women exhibiting signs and symptoms of threatened abortion whose pregnancy was of twelve weeks' duration or less. It has been pointed out in a previous communication that pregnandiol excretion is relatively constant in the first trimester (averaging 10 mg. per 24 hours).<sup>20</sup> Fluctuations in the second trimester of pregnancy are large (from 10 to 70 mg. per 24 hours with a rapid increase as pregnancy advances) and, therefore, the trend in excretion is difficult to determine. All cases with evidence of organic general or pelvic pathology were excluded in order to eliminate so far as possible nonendocrine factors contributing to the symptoms or the abortion.

### Results

Table I summarizes the results obtained in the analysis of 335 cases. In 155 (46 per cent) the symptoms subsided and the pregnancy continued undisturbed. One hundred and eighty (54 per cent) aborted within ten days of the last pregnandiol determination. Of this series of 335, normal pregnandiol excretion was found in 191 patients. Only 40 women in this group (21 per cent) aborted. Decreased excretion levels, on the other hand, were obtained in 144 patients. Practically all of these women aborted, only four patients (3 per cent) retaining the pregnancy.

TABLE I. SUMMARY OF RESULTS

PREGNANDIOL EXCRETION	NO. OF CASES	CLINICAL RESULTS			
		ABORTION		RETENTION	
		NO.	PER CENT	NO.	PER CENT
Normal	191	40	21	151	79
Decreased	144	140	97	4	3
Total	335	180		155	

Further analysis (Table II) reveals that 104 of the 191 patients excreting normal amounts of pregnandiol received no progesterone therapy. Seventy-seven per cent (80 women) retained the pregnancy. The remaining 87 patients received progesterone in some form, either oral or parenteral or both. The dosage during symptoms varied from 10 mg. of oral anhydrohydroxyprogesterone per day to 25 mg. of the parenteral preparation daily, and represents the range of amounts employed in current practice.<sup>6-9</sup> Eighty-two per cent of these women (71) retained the pregnancy. The difference in retention of 77 per cent in the untreated group and 82 per cent in the treated group is not statistically significant in this series. It appears, therefore, that the progesterone therapy employed in these quantities had no particular effect on the clinical course of threatened abortion associated with a normal pregnandiol excretion.

Decreased pregnandiol excretion was recorded in 144 women. One hundred and six received no progesterone therapy. Of this latter group 103 (97 per cent) aborted and only three women carried to term. The remaining 38 patients were treated with progesterone. Only one patient retained the pregnancy. It is evident, therefore, that progesterone therapy had no appreciable effect in this group of patients.

rationale and practicability of utilizing pregnandiol excretion levels in the urine as a criterion.

2. An analysis of 335 patients with threatened abortion is reported, correlating the pregnandiol excretion values and progesterone therapy with the clinical course.

a. One hundred ninety-one patients excreted normal amounts of pregnandiol (evidence of normal progesterone secretion). The incidence of retention of pregnancy in the treated (82 per cent) and untreated (77 per cent) cases in this group was essentially the same.

b. One hundred and forty-four patients excreted less than normal amounts of pregnandiol (evidence of diminished progesterone secretion). Ninety-seven per cent of these patients aborted with or without progesterone therapy.

3. The inadequacy of currently employed dosages of progesterone in this clinical state is suggested.

4. A rationale is outlined for estimating the amount of progesterone which will result in the excretion of normal amounts of pregnandiol in early pregnancy.

5. In a small series of cases of threatened abortion, progesterone was given in amounts estimated to substitute for the progesterone deficiency as reflected by diminished pregnandiol excretion. The results suggest that this therapeutic approach may permit the continuation of some pregnancies which would otherwise end in abortion.

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of progesterone elaboration. A deficiency of progesterone secretion in early pregnancy is manifested by decreased pregnandiol excretion. Therefore, an adequate replacement dose would appear to be that amount of progesterone which raises the pregnandiol level to the values observed in normal early pregnancy. The average pregnandiol excretion in normal early pregnancy is 10 mg. per 24 hours.<sup>19, 27</sup> When progesterone is administered to human beings a variable amount is recovered in the urine as pregnandiol according to the clinical state.\* Thus, when progesterone is given to a nonpregnant woman in the preovulative phase of the cycle, approximately 10 per cent appears in the urine as pregnandiol. The administration of progesterone to a pregnant woman, for reasons yet unknown, leads to about a 25 per cent conversion. In other words, the normal pregnant woman converts 15 per cent more of the progesterone into pregnandiol. In threatened abortion demonstrating decreased pregnandiol levels, one cannot predict whether the response to the administration of progesterone will result in a 10 or 25 per cent excretion of pregnandiol. In order to be sure, under any circumstances, that a normal excretion of at least 10 mg. of pregnandiol in 24 hours would be obtained in these patients, the daily dose of progesterone employed should approximate 100 mg. Therefore, the amounts of progesterone used in the series analyzed above (from 1 to 25 mg. per day) appear totally inadequate.

In an attempt to clarify first the question of adequacy of progesterone dosage, and second, the significance of persistent decreased pregnandiol excretion in early pregnancy threatened with abortion, the following study was initiated. A group of thirteen patients in the first trimester of pregnancy with symptoms of threatened abortion and two consecutive low pregnandiol values in forty-eight hours was hospitalized. Four patients received daily intramuscular injections of peanut oil. The other nine patients received 80 to 120 mg. of progesterone† in the same volume of peanut oil intramuscularly each day until symptoms subsided or abortion occurred. The four patients receiving peanut oil aborted within four to five days after initiation of therapy. Of the nine patients receiving adequate substitution doses of progesterone, four retained the pregnancy. The percentage of retention (45 per cent), even though the series is still small, seems to be significantly related to the therapy, considering that in the larger series discussed above, only 3 per cent carried to term. Studies on a larger number of cases are in progress to test these suggestive, but inconclusive, results. Details will be reported later.

This small series suggests that the use of adequate doses of progesterone may permit the survival of some pregnancies which, according to our criteria, would otherwise end in abortion. In addition, these observations imply that the excretion of small amounts of pregnandiol over a period of forty-eight hours in the presence of symptoms does not necessarily indicate that the pregnancy cannot be salvaged. Since pregnandiol excretion can be used as an objective guide in demonstrating the status of progesterone production, and since adequate progesterone dosage can be estimated, it appears that the approach to the treatment of threatened abortion might be guided along such avenues.

### Summary and Conclusions

1. The present report emphasizes the necessity for objective criteria in evaluating progesterone therapy in threatened abortion and indicates the

\*Observations from this laboratory to be published.

†The progesterone used in this study was generously supplied by Roche-Organon Inc., Nutley, N. J., and the Upjohn Co., Kalamazoo, Mich.

Venning in 1937 and various modifications of that technique have been described since. Dr. Guterman's method of assaying pregnandiol is apparently an improvement over that which has been used before. Certainly, in the light of this paper, it has positive value. Just as Venning and Browne carried the ball for pregnandiol in the early days, followed by Hamlin's carefully prepared contributions, we now have Dr. Guterman advancing in an equally splendid manner with hopes of attaching new importance to this interesting subject.

The subject of ovarian metabolism is one of the most fertile fields in obstetrics and gynecology for research, exclusive of cancer, because the woman's sex life is built around the ovary. If we have now a reliable means for measuring the metabolism of the ovary through pregnandiol excretion, Dr. Guterman has made a monumental contribution. However, we cannot lose sight of the fact that the excretion of pregnandiol is influenced by the quantity of progesterone normally present in the body of the woman, the amount present in the corpus luteum, the excretion capacity of the kidneys and the index of steroid conjugation by the liver. These glaring uncertainties remain with us. Until they are explained, we cannot place an accurate evaluation on pregnandiol excretion.

DR. A. S. TULSKY (Closing).—Because pregnandiol appears in the urine coincident with the period of progesterone secretion by the corpus luteum and placenta, and because the administration of progesterone leads to the appearance of pregnandiol in the urine of individuals who normally would not excrete pregnandiol, it appears reasonable to assume that pregnandiol is an excretion product of progesterone. Although biochemical studies reveal the presence of other urinary metabolic products of progesterone, pregnandiol is the principal excretion product. The evidence available from studies in the laboratory indicates that the method for pregnandiol estimation which we employ is as accurate and sensitive as any other method in current use.

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### Discussion

DR. ARTHUR K. KOFF.—This is the largest series of cases of threatened abortion studied to date. Consequently, the results have a statistical value. For the first time we have an accurate laboratory test which is of significance so far as the diagnosis, treatment, and prognosis of threatened abortion are concerned. For example, in any given case of threatened abortion, if the pregnandiol levels are normal (10 mg. or more), it is obviously unnecessary to treat such a case with progesterone. As a matter of fact, in such cases it is largely wasted therapy. On the other hand, if the pregnandiol levels are low, 5 mg. or less, we might reason that the pregnancy is not alive or that, if it is alive, there is deficient secretion of progesterone. Again, in a given case if the pregnandiol level is low we can check whether or not the pregnancy is alive by doing an Aschheim-Zondek or Friedman test. If the Friedman test is positive and the pregnandiol remains at a relatively low level, then I am of the opinion that the patient should be treated with large doses of progesterone. The suggestion that Dr. Tulsy makes is that 75 to 100 mg. should be the average dose if we expect the pregnancy to be maintained. On the other hand, if the Aschheim-Zondek test or the Friedman test is negative and the pregnandiol level is low, we can assume the pregnancy is not alive and there is no need to treat the patient. She should be allowed to abort spontaneously or curettage can be done. It is unwise to make predictions so far as treatment with large doses of progesterone is concerned. However, on the basis of the nine cases that Drs. Guterman and Tulsy presented, four of the nine with low pregnandiol levels carried to term. I believe that if a sufficient number of cases are studied, perhaps we will have a different figure of survival and instead of having an abortion incidence of 79 per cent when the pregnandiol level is low, it is very likely that we may have a survival rate of 40 per cent or over.

DR. A. J. MAUZEY.—The subject of pregnandiol excretion remains confusing and perplexing. As we see it, there are two difficulties. First, are we agreed that pregnandiol excretion is a reasonable index of progesterone metabolism? Second, do we have a reliable method for determining the excretion of pregnandiol?

With all due regard to Dr. Guterman for the excellent presentation tonight, there remains some question as to whether the preceding premises have been established. The fact is, we know very little about progesterone metabolism. We know, of course, from past experiments that when progesterone is given during the corpus luteum phase of the menstrual cycle, there is an increase in the amount of pregnandiol excreted. We know, also, that if progesterone is given during pregnancy, increased quantities of pregnandiol may be recovered from the urine. However, if progesterone is given during the first half of the menstrual cycle, the inactive phase, the amount of pregnandiol recovered is little or nothing. We know further that if progesterone is given throughout the menstrual cycle, the total amount of pregnandiol excreted may be actually decreased. Why is it, then, that the excretion of pregnandiol is definitely increased when progesterone is administered during corpus luteum and placental activity but is greatly reduced or absent altogether when the corpus luteum is in an impaired or nonfunctioning condition? Furthermore, pregnandiol is found in the urine of the human male and will be increased following the administration of progesterone, in spite of the absence of a corpus luteum. The substance is also present in the urine of cases of adrenogenital syndromes. These observations should caution us when placing an interpretation on pregnandiol excretion, particularly as it applies to prognosticating pregnant states.

As to the second premise, that of having a reliable method for measuring the amount of pregnandiol excreted, we wish to state that the first popular assay was reported by

Analyzing these figures, we see that 20 of the 23 patients who died had far-advanced tuberculosis. These 20 patients give a mortality of 46.5 per cent for the group of 43 far-advanced patients, whereas the mortality in the moderately advanced group is 5.7 per cent and there is no mortality in the minimal or arrested groups. There were 19 unimproved patients, only one of whom was worse. Many of these patients signed out of the hospital against advice, and since their condition was neither better nor worse, we have listed them as unimproved. Nine of the 43 patients with far-advanced tuberculosis, 21.2 per cent, were unimproved as were 9 of the 35 patients, 25.6 per cent, with moderately advanced tuberculosis.

Under "No Change" are included those patients whose condition before and for a period of three months after delivery was not altered. All the arrested cases are in this category as are three of the 21 minimal cases, making a total of 18 patients or 15.5 per cent of the 116 patients.

The largest number of patients, 56, or 48 per cent of the 116 cases, were improved following delivery. Comprising this category were 14 far-advanced cases, 24 moderately advanced cases, and 18 minimal cases.

The deleterious effect of pregnancy on the course of pulmonary tuberculosis has been emphasized by many writers.<sup>13, 16-21</sup> However, these authors fail to compare the results in the pregnant group with a nonpregnant group of women with similar tuberculous lesions. More recently a majority of writers, both phthisiologists and obstetricians, have stated that pregnancy does not have a harmful effect on tuberculosis.<sup>12, 22-28</sup> One of the most important factors responsible for the better results more recently obtained in the pregnant tuberculous patient is that the tuberculous disease is treated actively during the pregnancy. This treatment, in addition to the usual bed rest and proper diet, includes pneumothorax, the severing of adhesions and the performance of thoracoplasties during the pregnancy. This point cannot be emphasized too strongly, for we believe it is poor therapy to wait three to six months for a pregnancy to terminate before treating the associated medical condition with all the means at our disposal.

In the past few years four thoracoplasties have been performed in the fourth to seventh month of gestation, all with excellent results. In no case did an abortion or premature delivery occur. A number of cases of conception and delivery following thoracoplasty have been reported, the great majority showing excellent results.<sup>29-33</sup>

In a nonpregnant group of women treated at Sea View Hospital from 1939 through 1945, there were 4,455 patients, of whom 30.9 per cent died, compared to a mortality of 19.8 per cent in the pregnant group treated during this period. We do not assume from these figures that pregnancy had a beneficial effect on the course of pulmonary tuberculosis, nor do we advocate that pregnancy be contemplated to improve an existing tuberculous process. Several factors may explain the lower mortality in the pregnant group. First, the number of pregnant patients, 116, is small compared to the 4,455 nonpregnant patients, so that several deaths could produce a significant change in the smaller group. Second, becoming aware of their pregnancy, many women sought medical attention, so that the tuberculosis was diagnosed and treated earlier than occurred in the nonpregnant group. Many of the nonpregnant group were not aware of their tuberculosis until it was far-advanced and only then sought medical care. Such patients, whether pregnant or not pregnant, have a high mortality, as note our mortality of 46.5 per cent in the far-advanced pregnant group. Third, the number of our minimal and arrested cases, 36 of 116, or 31 per cent is much greater than the number of minimal and arrested cases for the hospital, as a whole. Since there were no deaths in the pregnant groups with minimal and arrested

## PREGNANCY AND TUBERCULOSIS

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THE increasing frequency with which tuberculosis is encountered during pregnancy makes the management of pregnancy so complicated an important obstetrical as well as phthisiological problem. The average incidence of tuberculosis when history and physical examination alone are used is 0.75 per cent,<sup>1-5</sup> whereas, when fluoroscopy and x-ray are included in the antepartum examination, the incidence of tuberculosis is approximately 2 per cent.<sup>6-8</sup> When one considers that the incidence of heart disease in pregnancy is between 2 and 3 per cent,<sup>9-10</sup> with a maternal mortality of less than 4 per cent,<sup>9-11</sup> but that the mortality of tuberculosis in pregnancy is from 20 to 35 per cent,<sup>12-14</sup> the management of the tuberculous pregnant woman takes on added significance.

In discussing the effects of pregnancy on tuberculosis one must take cognizance of the type and extent of the tuberculous lesions and compare a similar nonpregnant group of women before arriving at a conclusion. The classification of the National Tuberculosis Association into far-advanced, moderately advanced, minimal, and arrested disease is used in this report to denote the extent of the tuberculous process and the qualitative classification of Ornstein, Ulmar, and Dittler<sup>15</sup> is mentioned in discussing the type of the tuberculosis.

### Materials and Method

This report includes 116 deliveries in tuberculous patients whom we have personally attended at Sea View Hospital from 1939 through 1945. All of the patients were treated by the phthisiologists for their tuberculosis and received antepartum care by us. The average stay in the hospital before delivery was three months and the average time in the hospital after delivery was four months. The final result in a patient was determined after her discharge from the hospital or after a follow-up at home. In some instances, following delivery, a thoracoplasty was performed and the patient was not discharged for one year or more. In a small number of cases the patients signed out against advice within one month after delivery. There were 64 white, 50 Negro, and 2 Mongolian patients. The results in these patients are shown in Table I.

TABLE I. RESULTS IN PREGNANT PATIENTS WITH PULMONARY TUBERCULOSIS AS RELATED TO EXTENT OF DISEASE

EXTENT	NO. OF CASES	DIED	UNIM- PROVED	NO CHANGE	IMPROVED
Far-advanced	43	20	9	0	14
Moderately advanced	35	2	9	0	24
Minimal	21	0	0	3	18
Arrested	15	0	0	15	0
Osseous	2	1	1	0	0
Totals	116	23	19	18	56



TABLE IV. EFFECT OF DURATION OF LABOR ON PULMONARY TUBERCULOSIS

	DIED	UNIMPROVED	IMPROVED
Labor less than 8 hours	11	19	18
Labor 8 to 24 hours	2	3	6
Labor over 24 hours	2	1	1
Totals	15	23	25

than eight hours. Ten had a labor of from eight to twenty-four hours and only three had a labor longer than twenty-four hours. The comparatively high mortality in the patients who had a short labor, 23 per cent, is due in part to the fact that many of these patients had a premature delivery because of their septic condition. The mortality in the four patients who had a labor over twenty-four hours was 50 per cent.

### Analgesia and Anesthesia

More harm may result from the improper use of analgesia and anesthesia in the pregnant tuberculous woman than from using no anesthesia and analgesia at all. Alexander<sup>14</sup> states that the preoperative use of narcotic doses of such drugs as morphine, scopolamine, Amytal, and Avertin abolishes or greatly diminishes the cough reflex and the function of voluntary expectoration, not only during the operation, but for a number of hours afterward. During this time the stasis of the pulmonary secretions may cause the development of new areas of infection within the lung. Ether, chloroform, and Avertin are more dangerous than gas or local anesthesia from the point of pulmonary complications because of the relatively prolonged postoperative unconsciousness they produce, during which time the patient does not cough or expectorate efficiently.

In this series, analgesia was used in 35 patients. Morphine and scopolamine were avoided and the drugs most commonly used were Nembutal, paraldehyde and codeine and phenobarbital. No conclusions can be made concerning the efficacy of one drug over the other because the number of cases is too small and because other factors such as the type and extent of the pulmonary disease and the duration of labor must be taken into account. Anesthesia at the time of delivery consisted of local pudendal block in the large majority of cases with the occasional use of cyclopropane or nitrous oxide. In avoiding narcotic doses of drugs and general anesthesia, we have perhaps circumvented their ill effects on the tuberculous patient. This aspect of the problem requires careful individualization with a view to making the patient as comfortable as possible during her labor and yet not depressing her respiration to such an extent that she may suffer a spread of the tuberculosis.

### Cesarean Section in Pulmonary Tuberculosis

Because of the high mortality, 46.5 per cent, in pregnancy associated with far-advanced pulmonary tuberculosis, and because we could not foretell the duration of labor in primiparas with large or moderate-sized babies, we decided to do elective cesarean sections on primiparas with far-advanced tuberculosis. We noted that the results in our first fifteen cases were better than those in the group who were allowed to deliver spontaneously; therefore, we broadened our indications to include the less severe types of pulmonary tuberculosis. We have performed 53 cesarean sections, the results of which are shown in Table V.

In this group of 53 patients who had cesarean sections, 8 died and the mortality rate was 15 per cent. This compares favorably with the mortality of 23.8 per cent in the 63 patients who had spontaneous deliveries. Since most of our

tuberculosis, this would tend to decrease the mortality in the pregnant group as compared to the nonpregnant group.

In tuberculosis, as in most chronic conditions, the later the disease is diagnosed and treated, the poorer will be the end results. Table II shows the results in patients known to have tuberculosis before the onset of pregnancy compared with those women in whom tuberculosis was first diagnosed during the pregnancy.

TABLE II. RESULTS IN TUBERCULOSIS DIAGNOSED BEFORE AND DURING PREGNANCY

	BEFORE	DURING
Died	12	11
Unimproved or no change	27	10
Improved	38	18
Totals	77	39

In the 77 patients whose tuberculosis was diagnosed before the onset of pregnancy, 12, or 15.6 per cent, died compared to 28.2 per cent who died in the group diagnosed during pregnancy. Rist<sup>13</sup> reports a mortality of 51.2 per cent in 117 women whose tuberculosis was first diagnosed during or immediately following delivery.

### Effect of Parity on Pulmonary Tuberculosis

In our series there were 70 multiparas and 46 primiparas. The effect of parity on pulmonary tuberculosis is shown in Table III.

TABLE III. EFFECT OF PARITY ON PULMONARY TUBERCULOSIS

	MULTIPARAS	PRIMIPARAS
Died	14 or 20.0 per cent	9 or 19.5 per cent
Unimproved or no change	24 or 34.2 per cent	13 or 28.5 per cent
Improved	32 or 45.7 per cent	24 or 52.2 per cent
Totals	70	46

The percentages for multiparas, 20 per cent, and for primiparas, 19.5 per cent, are almost identical. Six per cent more multiparas showed no change in their condition than did primiparas, and about six per cent more primiparas were improved than were multiparas. We feel these small variations have no significance and believe that parity has no influence on the course of pulmonary tuberculosis.

### Effect of Duration of Labor on Pulmonary Tuberculosis

Most men are agreed that a long, hard labor is to be avoided in the woman with pulmonary tuberculosis, not only because the straining during labor may cause a spread of the disease, but also because the exhaustion and increased blood loss may so weaken her resistance as to cause an extension of the pulmonary disease. The duration of labor was recorded in the 63 patients having vaginal deliveries. Although we realize that the time element alone is not the only factor to be considered, and that several hours of severe, exhausting pains may be more harmful than a longer period of mild or moderate pains, only the time factor could be accurately recorded and used as a basis for comparison. Table IV shows the effect of the duration of labor on pulmonary tuberculosis.

Since it was our intent not to subject any patient to a prolonged labor wherever this was possible, most of the patients, 48 of 63, had a labor of less

currence of any of the toxemias of pregnancy, especially severe vomiting in the first trimester, and the history of previous labors. In our series of 116 patients, the parity seemed to have no influence on the end results. Of great importance, however, was the time when the tuberculosis was diagnosed and treated in relation to the pregnancy. When tuberculosis was known to exist before the pregnancy, the mortality was 15 per cent, in contrast to 29.1 per cent when the tuberculosis was first diagnosed during the pregnancy.

When we compare the end results in pregnant and nonpregnant groups with similar extent and type of tuberculosis, we find very little difference. As a matter of fact, the pregnant group had a lower mortality than the nonpregnant group. The best results were obtained when the tuberculosis and the pregnancy were treated concomitantly and adequately. Although no absolute routine can be given, experience has proved that the best results are obtained when we adhere to certain principles. Patients with moderately advanced, minimal, or arrested tuberculosis who have been controlled for a period of at least six months may be permitted to go into labor, provided no obstetrical contraindication exists, and to be delivered by forceps in the second stage. The pregnant woman with far-advanced tuberculosis must be carefully evaluated. In the multipara with a history of a short, easy previous labor, vaginal delivery may be awaited using forceps at complete dilatation. A primipara or a multipara with a history of long, severe labors should have a cesarean section under local or spinal anesthesia. A long period of bed rest, up to three months or more, as dictated by the tuberculous condition, is indicated after delivery for the tuberculous woman. For analgesia we have found Nembutal satisfactory and prefer local anesthesia at the time of vaginal delivery.

In some instances, even though the tuberculous woman comes through her pregnancy and labor without a flare-up, a breakdown in her pulmonary condition occurs at a later date. Any change in her condition due to parturition should become evident within two months after delivery; any change after that period should not be attributed to her pregnancy or labor. In all probability such exacerbations are due to the patient's undertaking too many household duties and neglecting her rest and diet. The sociological and financial aspects are, of course, to be considered and contribute to the deleterious effects incorrectly ascribed by some to the pregnancy.

### Conclusions

1. The incidence of tuberculosis complicating pregnancy when fluoroscopy and x-ray are used in the antepartum examination is approximately 2 per cent.
2. The maternal mortality in our series of 116 cases was 19.8 per cent; 87 per cent of the deaths occurred in the far-advanced group.
3. The mortality in the far-advanced group delivered by cesarean section was 33.3 per cent, whereas the mortality in the far-advanced group delivering spontaneously was 63.1 per cent.
4. Parity has no effect on pulmonary tuberculosis.
5. The mortality when tuberculosis is diagnosed during pregnancy is almost twice as great as when it is diagnosed before pregnancy.
6. The important factor in prognosis for the pregnant, as well as for the nonpregnant woman, is the extent and type of the tuberculous lesion and the rapidity with which treatment can be instituted.
7. Prolonged, severe labor is to be avoided in pulmonary tuberculosis.

TABLE V. RESULTS FOLLOWING CESAREAN SECTION IN PULMONARY TUBERCULOSIS

	DIED	UNIMPROVED	IMPROVED
Far-advanced	8	4	12
Moderately advanced	0	3	14
Minimal	0	0	5
Arrested	0	7	0
Totals	8	14	31

deaths, 20 out of 23, or 87 per cent, occurred in the far-advanced group, we compared our results in cesarean sections and spontaneous deliveries in this group. Table VI shows this comparison.

TABLE VI. RESULTS IN FAR-ADVANCED TUBERCULOSIS FOLLOWING CESAREAN SECTION AND SPONTANEOUS DELIVERY

	CESAREAN SECTION	SPONTANEOUS DELIVERY
Died	8	12
Unimproved	4	4
Improved	12	3
Totals	24	19

The mortality in the 24 patients with far-advanced tuberculosis who had cesarean sections was 33.3 per cent, whereas the mortality in the 19 patients who delivered spontaneously was 63.1 per cent. There were 16.6 per cent unimproved following cesarean section compared to 21 per cent unimproved following spontaneous delivery. Twelve of the 24 patients, or 50 per cent, were improved in the group who had cesarean sections compared to 3 of 19, or 15.8 per cent, in the group who delivered spontaneously.

We are not prepared to advocate cesarean section for all cases of pulmonary tuberculosis, but we are convinced that it has a definite place in selected cases. Patients with contracted or borderline pelves, patients with far-advanced tuberculosis, and patients who have had thoracoplasties during or before pregnancy should be carefully evaluated as to the advisability of a cesarean section. All the cesarean sections were performed under local or spinal anesthesia with the use of phenobarbital as preoperative medication.

Condition of Infants

There were 117 infants born to the 116 patients, including one set of twins. The twins were born prematurely and one twin weighing less than three pounds died. Only one other infant died and this was the child of a patient in whom the fetal heartbeat was lost two weeks before delivery. There were 115 infants who were normal with an average birth weight of seven pounds. None of the infants showed any evidence of tuberculosis and no case of tuberculosis of the placenta was encountered in this series, although we had found one case of tuberculosis of the placenta in a previous series.<sup>35</sup> McCord<sup>36</sup> describes a case of direct intra-uterine transmission of tuberculosis from mother to baby. In all our cases the infants were removed to the pediatric building immediately after delivery and the mother was not permitted to breast feed the infant.

Discussion

The treatment of the pregnant woman with tuberculosis must be individualized in that one must differentiate the extent of the tuberculous lesion and the obstetrical complications. Among the latter must be considered the presence of any cephalopelvic disproportion which may cause a prolonged labor, the oc-

## EXPERIENCE WITH EXTRAPERITONEAL CESAREAN SECTION AT THE UNIVERSITY OF IOWA HOSPITALS

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TWO previous reports<sup>1, 2</sup> have summarized the cesarean section experience at the University Hospitals up to and including the year 1942. Since that time the Waters<sup>3</sup> extraperitoneal operation has been added to the techniques available for abdominal delivery. It is still uncertain whether this operation offers any real advantage in the grossly or potentially infected patient, but our limited data are presented to assist with its final evaluation.

The clinical management of prolonged labor is not yet standardized and several plans are under trial in different clinics.

1. McKelvey<sup>4</sup> feels that physicians should be able by clinical and x-ray pelvimetry to forecast the probable course of parturition prior to its onset, and that trial labor has little place in modern obstetrics. As a result of this philosophy, his incidence of cesarean section is relatively high.

2. Dieckmann,<sup>5</sup> at the Chicago Lying-in Hospital, evaluates these borderline patients at the end of twenty-four hours of labor or after eighteen hours of ruptured membranes. This short trial labor allegedly provides sufficient time to study the course of labor, does not jeopardize the patient, and reduces the incidence of cesarean section. He feels that low segment cesarean section cannot be done with safety after this interval. Patients who have been in labor longer than twenty-four hours and who require intervention are treated by cesarean hysterectomy, Dührssen's incisions with midforceps, or some type of destructive procedure. It is his opinion that extraperitoneal cesarean section has no real place in modern obstetrics, particularly in the grossly infected patient.

3. Other clinics feel that extraperitoneal cesarean section is the procedure of choice if vaginal delivery does not seem feasible in the grossly or potentially infected patient. By waiting beyond Dieckmann's time limit, many patients can be successfully delivered vaginally. The additional time consoles the operator who no longer has to choose between sacrificing the uterus of a primipara or doing a destructive procedure on a live child or on one who has died from an unsuccessful attempt at forceps delivery.

4. Randall,<sup>6</sup> at the Mayo Clinic, is extending the use of the low flap operation to include patients who have been in labor forty-eight hours or longer. He feels that the apparent safety of the extraperitoneal operation is due to use of the new therapeutic agents, such as antibiotics, chemotherapy, and blood.

5. Eastman<sup>7</sup> and others are forcing labor with Pituitrin in selected cases of prolonged labor without disproportion. In such cases the judicious use of this drug has reduced the incidence of cesarean section 50 per cent and of midforceps 60 per cent. The use of Pituitrin admittedly involves some risk, but it is minimal if contraindications such as disproportion and grand multiparity are observed.

8. Nembutal for analgesia and local anesthesia has given good results in our cases.

9. Cesarean section has a definite indication in selected cases of tuberculosis.

10. None of the infants born had evidence of prenatal or postnatal tuberculosis. The infant mortality was 1.7 per cent.

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etry were of little value in determining the method of delivery prior to the onset of labor or even early in labor. According to clinical measurements, eighteen of the twenty-six patients in labor had normal pelves, five generally contracted, one simple flat, and two funnel. The majority of these patients were studied by x-ray pelvimetry (triangulation method), but only one revealed significant pelvic contraction.

TABLE II. INDICATION FOR EXTRAPEITONEAL CESAREAN SECTION

ELECTIVE TYPE—30		PATIENTS IN LABOR—26	
Repeat sections	24	Prolonged labor	15
Primary	6	Uterine inertia	10
1 Placenta previa		Disproportion	7
1 Transverse presentation		Failure forceps	2
1 Generally contracted pelvis		Repeat section	2
2 Funnel pelvis		Toxemia	1
1 Toxemia		Transverse presentation	1
		Face	1
		Brow	1
Total	30	Total	40

Twenty-one of the twenty-six patients in labor were primigravidas. At the time of intervention, the fetal positions were occiput transverse 11, occiput posterior 10, face 1, brow 1, occiput anterior 1, breech 1, and transverse (shoulder). 1. The average preoperative period of labor was forty hours, the longest being 96 hours. The average duration of ruptured membranes was thirty hours. The cervix was 3 to 5 cm. dilated in nine instances and more than 5 cm. in fifteen. Complete dilatation was present twice. The presenting part was usually above the spines.

Seventeen of the patients in labor were grossly infected according to the criteria of Cosgrove<sup>8</sup> (prolonged labor, membranes ruptured for forty-eight hours, evidence of infection manifested by intrapartum chills, rapid pulse, and elevation of temperature). Intrapartum fever occurred in eight of the twenty-six. All but one of the women with intrapartum fever had febrile puerperia; one had marked parametritis, and another femoral thrombophlebitis.

Eighteen physicians performed the fifty-six operations; more than half were done by residents; no single physician did more than twelve. It is believed that the average resident, after assisting with several and after doing two or three under supervision, can reasonably perform the operation.

Spinal anesthesia was used in 41 cases, cyclopropane in thirteen, and caudal twice. In certain early cases inhalation anesthesia was utilized, but was soon abandoned since the long operative time made it difficult to resuscitate the baby.

The operative technique was similar to that described by Waters.<sup>3</sup> The operators generally preferred not to open the peritoneal cavity to facilitate the dissection. Failure to drain the space of Retzius was not followed by an increased incidence of wound infections or serious complications.

The midline abdominal incision was used 33 and the transverse 23 times. Wound infection occurred in 30 per cent of the transverse incisions (the patients not in labor), while none of the midline incisions became infected. Faulty hemostasis and heavy panniculus were the principal factors inclining to wound infection in the former.

The average operative time was one hour and thirty-seven minutes, the longest two hours and fifty minutes, the shortest one hour. In Waters'<sup>9</sup> first group the average total operative time was sixty minutes, but later this was reduced to thirty-eight minutes. The operative time of seventy-three minutes reported by Daichman<sup>10</sup> more nearly approximates our own. This type of

Between July 1, 1926, and December 31, 1947, cesarean section was performed 362 times in a series of 20,416 deliveries, an incidence of 1.8 per cent. There were five maternal deaths, a mortality of 1.4 per cent. The last maternal death associated with cesarean section occurred in May, 1940. The last 188 consecutive operations have been performed without a death in the hospital, but in 1944 one patient died at home from a massive pulmonary embolus two days after her return home.

Table I shows the types of cesarean section done between January, 1940, and December, 1947. Despite fluctuations in the number of deliveries from year to year, the number of abdominal deliveries annually has remained fairly constant with the incidence ranging from 1.2 to 4.0 per cent. The ratio of cesarean sections to total deliveries reached its highest peak (1 in 25) during 1947, due to an increase in the number of repeat operations and to the development of a more liberal attitude toward abdominal delivery.

TABLE I. TYPE OF CESAREAN SECTIONS  
JANUARY, 1940, THROUGH DECEMBER, 1947

	TOTAL DELIVERIES	TOTAL SECTIONS	PER CENT SECTIONS	TYPE OF CESAREAN SECTION			
				CLASSICAL	LOW CERVICAL	CESAREAN HYSTEREC- TOMY	EXTRA- PERITONEAL
1940	1913	23	1.2	18	3	2	0
1941	1678	21	1.3	12	5	3	1
1942	1287	19	1.5	7	5	4	3
1943	870	25	2.8	10	8	2	5
1944	588	19	3.2	3	12	1	3
1945	592	20	3.4	0	7	1	12
1946	874	25	2.8	1	7	0	17
1947	991	40	4.0	5	20	1	14

During the four years from 1940 through 1943, the classic operation was the procedure of choice. Since 1944, this technique has been employed only on the occasional patient not in labor, who had placenta previa or transverse presentation. The low flap cesarean section is now more generally used. The first extraperitoneal operation in the University Hospitals was performed in 1941. In 1945 and 1946, it was the most commonly employed procedure for abdominal delivery. In repeat operations the extraperitoneal approach was chosen solely for resident staff training. During 1947, the distribution of the various types has been more equitable. Since adoption of the extraperitoneal approach, cesarean hysterectomy has been reserved for patients with ruptured uterus, severe degrees of ablatio placentae, and large myomas necessitating abdominal delivery.

The fifty-six extraperitoneal sections represent one-third of all abdominal deliveries since 1941. Thirty were performed on patients not in labor and twenty-six after parturition had started. The majority (nineteen) of the latter went into labor spontaneously but seven had labor induced with artificial rupture of the membranes.

Table II shows the indications for the extraperitoneal cesarean sections. Twenty-four of the thirty women not in labor had had previous abdominal deliveries; the remainder had placenta previa, transverse presentation, toxemia, or pelvic contraction. Certain of the twenty-six patients in labor presented multiple indications as shown in the table. Clinically, most of these patients had prolonged labors on the basis of uterine inertia. Clinical and x-ray pelvim-



TABLE III. SUMMARY OF RECENT EXTRAPERITONEAL CESAREAN REPORTS

NAME	TYPE		TOTAL	MATERNAL DEATHS	FETAL DEATHS	BLADDER INJURIES	PERITONEAL INJURIES	COMPLICATIONS	DRAINAGE	INFECTED CASES
	WATERS	LATZKO								
Aldrich <sup>12</sup>	0	40	40	1*	No note	No note	No note	No note	No note	No note
Cosgrove	323	0	323	3*	No note	4	68	No note	Yes	90
Daichman <sup>10</sup>	100	0	100	0	2	17	36	10 Wound infect.	Yes	76
Eisaman <sup>13</sup>	22	0	22	0	0	1	3	1 Phlebitis	Yes	12
Hanley <sup>14</sup>	40	0	40	0	1	1	20	1 Wound infect. 1 Phlebitis	No note	No note
Irving <sup>15</sup>	59	40	99	3*	No note	No note	No note	No note	No note	No note
Irwin <sup>16</sup>	0	32	32	0	No note	4	5	5 Wound infect.	Yes	18
Keettel	56	0	56	0	3	1	23	9 Wound infect. 1 Phlebitis	No	17
Norton <sup>17</sup>	0	160	160	3*	9	9	44	No note	No note	160
Pieris	65	0	65	0	0	3	7	No note	No note	6 Out of 20 cases
Ricci <sup>19</sup>	175	0	175	1*	7	6	No note	3 Phlebitis	No	No note
Stearns <sup>20</sup>	16	0	16	0	2	3	7	No note	No note	13
Williamson <sup>11</sup>	0	25	25	0	2	0	8	3 Wound infect. 3 Phlebitis	No note	8
Total	855	297	1152	11*	25	49	220	30 Wound infect. 11 Phlebitis		399

\*Five due to sepsis.

operation requires more time from the initial incision until the baby is delivered, than other types. In this series this time averaged forty-eight minutes; the longest was seventy-eight, and the shortest twenty minutes.

The peritoneum was opened twenty-three times, 39 per cent, not including the cases where it was done purposely to permit tubal ligation. The bladder was injured only once, on the first case.

The blood loss was the same as with other types of abdominal deliveries but two recent patients lost more than 600 c.c. of blood. Williamson<sup>11</sup> warns of the danger of hemorrhage and mentions blood loss as the cause of several extraperitoneal cesarean section deaths.

Postpartum oral temperatures were taken every four hours, and any elevation to 100.4° F. excluding the first twenty-four hours was considered "febrile." By such a criterion, the puerperium was febrile in 60 per cent of the patients in labor and in 50 per cent of those having elective operations. The majority of the fevers were of short duration; only five lasted beyond the fifth day. This approximates the cesarean section morbidity of 57.5 per cent reported from this clinic by Wentsler and Stout.<sup>2</sup>

Thirty-two patients had uncomplicated convalescences. Abdominal distention was noted twenty times, nasal suction was required in eight instances. In the majority of these cases the peritoneum had not been opened and there was no evidence of peritonitis. The ileus was probably due to splinting of the abdomen because of abdominal discomfort. Blood transfusions were given to eighteen patients, penicillin to twenty, and the sulfonamides to ten. The average hospital stay was twelve days, the longest being forty-five days.

There were no maternal deaths. The infant mortality was 5.3 per cent, two neonatal deaths and one stillbirth. Two children with convulsions presented signs of intracranial hemorrhage but survived and seemed normal at discharge. Two women were critically ill as follows:

CASE 1.—Hospital Number 43-2142, aged 20 years, was a primigravida in labor twenty hours, with membranes ruptured eight hours, no vaginal examination, afebrile. Abdominal delivery was indicated by cephalopelvic disproportion. The operative time was sixty minutes, there was no injury to the bladder or peritoneum, the blood loss was less than 300 c.c. Post-operatively, there was a severe puerperal infection with signs of peritonitis. The patient was irrational and critically ill for six days. Several intrauterine cultures revealed beta hemolytic streptococci in pure culture.

CASE 2.—Hospital Number 45-787, aged 25 years, a primigravida, had a trial labor of nine hours with intact membranes, one sterile vaginal examination, no fever. Operative time was two hours and thirty minutes under inhalation anesthesia, the child was severely asphyxiated and had intracranial hemorrhage, but survived. The mother developed either pulmonary embolism or atelectasis soon after operation, and on the following day presented signs of severe infection (not pulmonary). She was acutely ill for several days.

The abdominal delivery of a stillborn child is usually a clinical error. Our patient had been in labor eighty-seven hours before operation, the fetal heart was allegedly heard on one occasion. A flat film of the abdomen, read later, revealed evidence of fetal death. The child showed maceration.

One neonatal death occurred fifteen hours after birth by elective cesarean section; post-mortem examination showed pulmonary atelectasis. The other neonatal death represented a real tragedy. The mother had lost two previous children, one an unexplained antenatal death, and the second because of vasa previa with hemorrhage. After a short trial labor, she was delivered abdominally because of lack of cervical dilation and failure of descent of the head. The child weighed 3,900 grams and did well until the tenth day when he was found dead in the bassinet. Postmortem examination revealed congenital cardiac disease, but asphyxia from aspirated food was suggested as the immediate cause of exitus.

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### Addendum

During 1948, there were twenty-nine abdominal deliveries; seven were extraperitoneal sections. Four of these patients were grossly infected but there were no infant or maternal deaths.

### Discussion

Table III summarizes various recent reports on extraperitoneal cesarean sections. Among 1,152 operations, there were eleven maternal deaths, a mortality rate of 1.0 per cent. Only five deaths were attributed to infection. The supravescical approach was used in 855 patients with six deaths, 0.7 per cent, the paravescical (Latzko) in 297 with five deaths, 1.6 per cent.

Unfortunately, some reports do not give the number of patients with pre-operative evidence of infection. However, in 753 cases where such data are available, 399, 54.3 per cent, were grossly infected according to Cosgrove's<sup>8</sup> criteria. There were six deaths in the entire group, a mortality of 0.8 per cent, but it is not clear whether all the fatalities occurred in the infected cases. Even if this is assumed, the death rate still would be only 1.5 per cent.

There were 25 infant deaths, 3.8 per cent, among 658 operations. Considering that many of these women had prolonged labors and in some cases had had attempts at delivery from below, the infant death rate is low.

The bladder was entered 49 times, 4.9 per cent, while the peritoneum was injured 220 times, 26.0 per cent. Wound infection and phlebitis were the most common postoperative complications.

Our experience with the extraperitoneal operation compares favorably with that of others except that the infant mortality is too high, considering that the operation was frequently done for fetal indications. The extraperitoneal approach allows a longer time for evaluation of the patient's ability to deliver herself, but, as with other types of abdominal delivery, too great delay may jeopardize both mother and child. Usually long labors are permitted only in patients with uterine inertia without disproportion.

Many questions concerning the extraperitoneal cesarean section remain to be answered, but our results with the operation in grossly and potentially infected patients requiring abdominal delivery appear to justify continued use of the technique. From 1935 to 1940, there occurred two maternal deaths associated with cesarean section; both women had prolonged labors, were grossly infected at the time of intervention, and were delivered by cesarean hysterectomy. Both received blood transfusions and one was given sulfonamides; both died of peritonitis. Since 1940, seventeen similar cases have been treated by extraperitoneal operation instead of cesarean hysterectomy without a death.

### Summary

1. A review of fifty-six extraperitoneal cesarean sections is presented.
2. There were no maternal deaths. Three children did not survive, an infant mortality of 5.3 per cent.
3. Our results with the supravescical extraperitoneal cesarean section have been sufficiently satisfactory to justify our continued use of the procedure in grossly and potentially infected patients requiring abdominal delivery.

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Forty-eight cases had adequate follow-up study. Of these patients, thirty-one expired in an average of eighteen months; in ten, the prognosis was stated as "poor," because of metastases or recurrence. Thus, 41 of 48 cases were in the nonsalvageable category. Only three patients were living and well five years postoperatively.

### Case Reports

**CASE 1.**—A. E., a 47-year-old Negro woman, first entered the hospital June 15, 1946, complaining of pain in the lower abdomen, of seven days' duration, nausea and vomiting for four days, and increasing size of the abdomen for eight months. The last menstrual period had occurred three years previously.

**Physical Examination:** A nontender cystic mass, arising from the left adnexa, extending to the level of the iliac crest, was found. Diagnosis of ovarian cystoma was made.

**Operation:** Bilateral salpingo-oophorectomy and subtotal hysterectomy were performed on June 24, 1946.

**Pathologic Report, Gross:** The left tube consisted of a 15 by 5 cm. cystic mass. The right tube was slightly dilated. **Microscopic:** The left Fallopian tube contained primary papillary adenocarcinoma, Grade II, and metastases to the myometrium and peritoneal fat were noted. The endometrium and ovaries contained no lesions.

**Subsequent Course:** The patient re-entered the hospital in November, 1946, with ascites and a palpable abdominal mass, her decline was rapid, and she expired in January, 1947. Consent for postmortem examination was denied.

**CASE 2.**—L. B., a 65-year-old, white woman entered the hospital Sept. 25, 1946, complaining of obstipation, anorexia, and weakness of five days' duration, and of a mass, increasing in size, in the lower abdomen, of eight months' duration. There had been no vaginal discharge or bleeding since the menopause fifteen years previously.

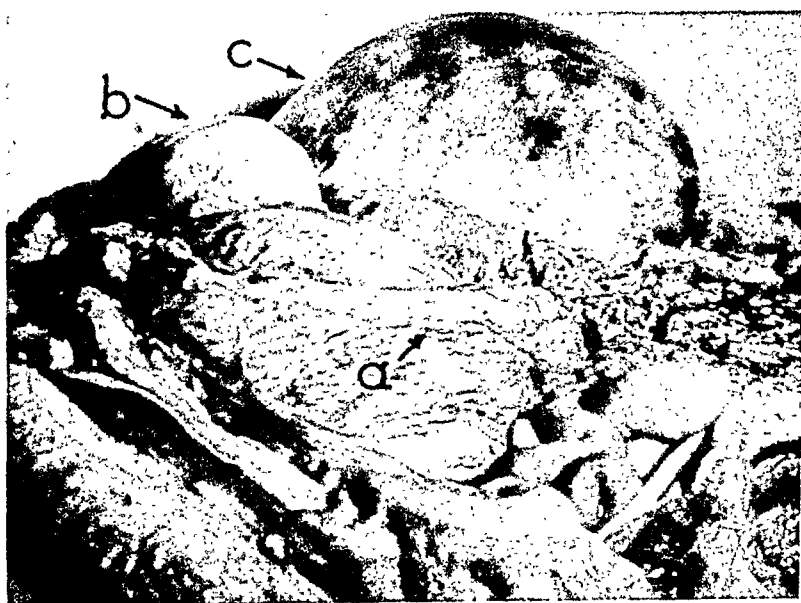


Fig. 1.—Note sausage-shaped left tube (a) running over anterior surface of mass, in which it is involved distally. Mass in center is a calcified, pedunculated fibroid (b). Large cystic mass on right (c) contained black serous fluid. Note peritoneal implants.

**Physical Examination:** An irregular mass that filled the left lower abdomen, and a separate mass that extended from the right adnexa to above the umbilicus were found. Diagnoses of fibromyomas of the uterus and right ovarian cystoma were made.

**Surgery:** was refused by the patient, her decline was rapid, and she expired Sept. 31, 1946.

## PRIMARY CARCINOMA OF THE FALLOPIAN TUBE

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PRIMARY carcinoma of the Fallopian tube is considered a rare entity. This is relatively true, but its occurrence is probably more common than was previously held. In 1888, Orthmann described the first case; since that time, 450 cases have appeared in the literature, with an increasing number in North American publications during the past two decades.

The diagnosis has been mainly dependent upon the observations of the pathologist, for, clinically, primary tubal cancer is extremely difficult to recognize. It is most frequently confused with ovarian tumors, fibromyomas of the uterus, and pelvic inflammatory disease, in that order of frequency.

Pathologically, the gross and microscopic appearance of adenocarcinoma of the tube may so closely simulate papillary adenocarcinoma of the ovary that the latter diagnosis is probably often erroneously made simply because of its known higher frequency. If, however, primary carcinoma of the tube were to be considered in every malignancy of the adnexa, and if multiple sections of the tube were to be examined, this lesion would undoubtedly be reported more often.

Sixty-one cases of primary carcinoma of the tube, appearing in the North American literature during the last sixteen years, have been reviewed and analyzed.

The average age of the patients was found to be 49.5 years, with extremes of 18 and 80 years.

The chief complaints were: (1) vaginal discharge, usually bloody (37 cases, or 61 per cent); (2) low abdominal pain (17 cases, or 28 per cent); (3) abdominal enlargement (4 cases, or 7 per cent). The average duration of symptoms was seven months, with extremes of three days and three years.

Most patients (52 cases, or 85 per cent) had a pelvic mass, of varying size and shape, usually nontender and firm. Five cases had no palpable mass, and four cases had "thickened adnexa."

The correct diagnosis was made preoperatively in only two cases.

The gross pathological description was almost invariable. The tubes appeared elongated and dilated, and were usually involved distally in a cystic mass, which contained yellow, cheesy material or brown, serous fluid. The fimbriated end of the tube was usually closed or indiscernible. On gross inspection, at the time of surgery, a diagnosis of hydrosalpinx was often incorrectly made.

The lesion arose most frequently from the distal one-third of the tube. Histologically, the commonest type was a papillary adenocarcinoma. In 15 cases (25 per cent) the lesion occurred bilaterally.

(Fig. 2). Hyperchromatic nuclei of various sizes and mitotic figures were present (Fig. 3).  
*Diagnosis:* Primary adenocarcinoma of the Fallopian tubes.

**CASE 3.**—P. W., was a 36-year-old Negro woman, who entered the hospital Dec. 12, 1946, complaining of intermenstrual bleeding of three months' duration, and of a mass, increasing in size, in the lower abdomen, of six months' duration. The last menstrual period had occurred two weeks prior to entry.

*Physical Examination:* A mass filling the pelvis and lower abdomen was found. A diagnosis of fibromyomas of the uterus with degeneration was made.

*Operation:* Bilateral salpingo-oophorectomy and subtotal hysterectomy were performed on Dec. 26, 1946. The uterus contained several small fibromyomas, and both tubes were dilated.

*Pathologic Report, Gross:* The right tube and ovary were incorporated in a cystic mass 10 cm. in diameter. The left tube was dilated to 1 cm. in diameter. *Microscopic:* Both tubes showed masses of adenocarcinoma replacing the mucosa, but the muscle layers were not involved. There was no evidence of malignancy in the endometrium or ovaries.

*Subsequent Course:* The patient was last seen in November, 1947, at which time a new palpable mass in the left adnexal region was found, which, clinically, was thought to be a recurrence.

**CASE 4.**—B. L., a 34-year-old Negro woman, entered the hospital July 14, 1947, with complaints of menometrorrhagia and abdominal pain of three months' duration. The last menstrual period had occurred three weeks prior to entry.

*Physical Examination:* Tenderness throughout the lower abdomen and a mass in the left adnexa were found. The corpus was slightly enlarged. Diagnoses of fibromyomas of the uterus and exacerbation of chronic pelvic inflammatory disease were made.



Fig. 4.—Note clusters of large cells with abundant clear cytoplasm at base of central tubal villus and change in epithelium along edge of large tubal fold on right. ( $\times 80$ )

*Operation:* Bilateral salpingo-oophorectomy and subtotal hysterectomy were performed on Oct. 15, 1947. The uterus contained small fibromyomas and both tubes were dilated.

*Pathologic Report, Gross:* The right tube was 11 cm. in length; the fimbriated end was clubbed, but the lumen was present. The left tube was 18 cm. in length, and varied from 5 mm. to 11 mm. in diameter. The infundibular portion formed a cystic mass 10 cm.

*Pathological Report, Gross:* Both pulmonary arteries were occluded by emboli. The left common iliac vein contained a large thrombus. Both tubes were markedly dilated in the ampullary and infundibular portions. Both became confluent with large cystic masses (Fig. 1). The distal portion of the left tube contained yellow-white caseous material, and



Fig. 2.—Section from proximal one-third right tube of Fig. 1. Shows abrupt change from regular epithelium to papillary type adenocarcinoma. ( $\times 80$ )

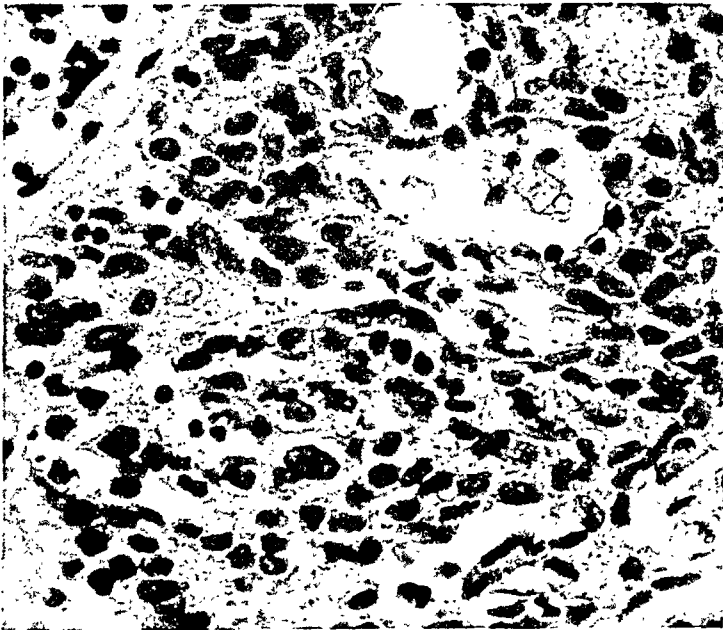


Fig. 3.—High power of largest nest of cells seen in Fig. 2. Shows hyperchromatic nuclei of various sizes and mitotic figures. ( $\times 300$ )

the mass on the right contained black serous fluid. *Microscopic:* Throughout the left tube, there were nests of anaplastic cells with occasional adenoid appearance. The distal two-thirds of the right tube contained a similar lesion, but a section from the proximal one-third showed an abrupt change from regular epithelium to an anaplastic papillary adenocarcinoma



CASE 5.—L. S., was a 44-year-old white woman who entered the hospital Sept. 1, 1947, complaining of a suprapubic mass, a bloody vaginal discharge, and left lower abdominal pain of four months' duration. The menses had been irregular during the previous four years.

*Physical Examination:* A firm, tender mass filling the lower abdomen was noted. Diagnoses of fibromyomas of the uterus and chronic pelvic inflammatory disease were made.

*Operation:* Bilateral salpingo-oophorectomy and subtotal hysterectomy were performed on Sept. 10, 1947. The uterus contained small fibromyomas, the right tube was dilated.

*Pathological Report, Gross:* The right tube was a sausage-shaped structure, measuring 10 cm. in length, and 0.4 cm. to 1.5 cm. in diameter. The distal portion was a multilocular cystic mass, measuring 15 cm. by 10 cm. This was filled with cheesy material and brownish yellow fluid. *Microscopic:* The right tube contained folds of flattened mucosa but part of the epithelial surface extended into the solid tumor (Fig. 6). The left tube, ovaries, and endometrium were not involved. *Diagnosis:* Papillary adenocarcinoma of the distal one-third of the right tube.

### Discussion

The five cases presented here were seen during 1946 and 1947. Compared with other reports, this is an unusually high number for so short a period of time. In these years, there were 3,606 gynecological admissions to the hospital.

In the cases here, the average age was 46, with extremes of 34 and 64 years. The chief complaints were abdominal enlargement, unusual vaginal bleeding, and low abdominal pain, in that order of frequency. Two patients presented themselves with symptoms suggestive of mechanical bowel obstruction. All cases had a palpable pelvic mass, and the most common preoperative diagnosis was "fibromyomas of the uterus." Carcinoma of the tube was not considered.

The clinical picture thus simulates many pelvic disorders of the woman near the menopausal age. However, primary carcinoma should be particularly considered when a dilated sausage-shaped tube is observed at the time of surgery. The distal portion is usually involved in a cystic mass. A specimen with this appearance should be opened prior to completion of the surgical procedure, and, if suspiciously malignant, should be immediately examined microscopically. This will preclude a diagnosis of a benign lesion, and will assure adequate surgical treatment.

Most authors of the reports reviewed agree that total hysterectomy and bilateral salpingo-oophorectomy is the operative procedure of choice. Although its efficacy is not established, most of the cases were treated by radiation therapy, postoperatively.

The microscopic appearance of the lesion is that of an adenocarcinoma, usually of Grade II or III. The most common variety is the papillary type. The criteria by which the lesion is determined as primary in the tube are, first, a change from normal to malignant epithelium (seen in Fig. 2); second, no invasion of the muscle layers of the tube by the neoplastic cells (seen in Fig. 6); and, third, no evidence of primary lesion in the ovaries or endometrium.

At times, primary carcinoma of the tube may be indistinguishable from primary papillary carcinoma of the ovary. In these cases it is urged that the pathologic report include at least the possibility of a tubal source. During this study, several such questionable cases were encountered.

The lesion spreads by direct extension and peritoneal implantation. Metastases apparently occur late. The site of predilection could not be determined, but no instance of metastasis to bone was encountered.

in diameter. The lumen was patent proximally, but the ampullary and infundibular portions were occluded by yellow, caseous material. *Microscopic:* The right tube, right ovary, and endometrium showed no evidence of malignancy. The left ovary contained one small area of adenocarcinoma beneath the surface. The proximal portion of the left tube contained clusters of large carcinomatous cells scattered throughout the tubal mucosa (Fig. 4). In



Fig. 5.—Sections taken from more distal portion of tube shown in Fig. 4. Mucosa now entirely replaced by tall folds of high columnar cells which contain various-sized nuclei and mitotic figures. ( $\times 300$ )



Fig. 6.—Lumen filled with papillary adenocarcinoma that does not invade muscle layer. Folds of tube are flattened, but part of the epithelial surface extends into the solid tumor. Cells have a large pink-staining vacuolated cytoplasm. ( $\times 10$ )

the distal portion of the tube, these cells completely replaced the mucosa and formed tall folds of high columnar cells that contained various sized, hyperchromatic nuclei with many mitotic figures (Fig. 5). *Diagnosis:* Primary adenocarcinoma of the left Fallopian tube.

*Subsequent Course:* Radiation therapy was begun Nov. 14, 1947, and when seen in February, 1948, the patient was well.

# APPLICATION OF THE VAGINAL SMEAR TO THE DIAGNOSIS OF PREGNANCY

## Preliminary Report

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PREGNANCY, from the moment of conception, produces an ovarian state and as such should be recognized in the vaginal smear. It is of utmost importance to establish such a diagnosis during the critical period of an ectopic gestation, not to speak of the many possible gynecological conditions from which it is often necessary that it be differentiated.

Vaginal smears in pregnancy have been described,<sup>1, 2</sup> emphasis being laid upon the specific cells which appear. Most often mentioned are the navicular cells with "enlargement and elongation of their nuclei and thickening of their surface membranes." It is, however, admitted that the recognition requires great experience and is not always dependable because similar cells may be found during the normal cycle.<sup>3</sup>

In the examination of the vaginal smears as they vary in physiological conditions, analysis is far simpler than one is led to believe from the cellular elements involved.<sup>4</sup> This also applies to pregnancy smears as they appear from the time of conception. A direct solution to a problem is desirable; facility of procedure<sup>5</sup> is attractive, especially if results are immediate. But no test should be more than a corroboration of associated findings. From such a viewpoint the following experiences and results are described in the hope that further study may substantiate the stated results.

From the beginning of this study, pregnancy smears, especially those obtained soon after conception and later confirmed, were examined repeatedly. A definite pattern was discernible but no isolated criteria seemed obvious. Further studies on smears before other "tests" were done resulted in correct "guesses" as well as incorrect ones. It soon became evident that negative pregnancies were correctly diagnosed but the positive cases were too often in doubt. On the other hand, these doubtful positives always revealed themselves in findings originally overlooked after pregnancy was confirmed. The difficulty in isolating features common to all remained a stubborn obstacle for a long time. Correct positives which increased in number were attributed to "hunch."

It was soon decided that (1) in the premenopausal delayed or missed period, the widespread differences between ovarian physiological activity and

\*Vaginal smears were prepared by obtaining the secretion with a pipette and smearing thinly on a slide. Immediate emersion in alcohol 95 per cent and ether equal parts, for several minutes is necessary in order to preserve the identity of cells. Differential staining can be accomplished within a few minutes by the use of a simple differential stain (by Shorr). The specimens illustrated were stained with an experimental stain, DF 77 A (by Papanicolaou). In general, cornified cells are revealed as red cells, all others are blue.

The writer acknowledges with thanks the . . . . . given him by Dr. George N. Papanicolaou as well as his generous supply of his . . . . . stain. He also wishes to thank Schering Corp., Bloomfield, N. J., for supplying Shorr's Differential Stain.

### Summary and Conclusions

1. Primary carcinoma of the Fallopian tube is a rare lesion, but it is more common than previously believed.
2. Five cases were seen, during 1946 and 1947, in this hospital.
3. Clinically, the diagnosis is extremely difficult to make. However, it should be particularly considered whenever a dilated, elongated tube, involved distally in a cystic mass, is observed at the time of surgery.
4. The microscopic appearance is usually that of a papillary adenocarcinoma.
5. The prognosis is poor.

### Addendum

Since the original report, another case was seen and the patient operated upon in March, 1948.

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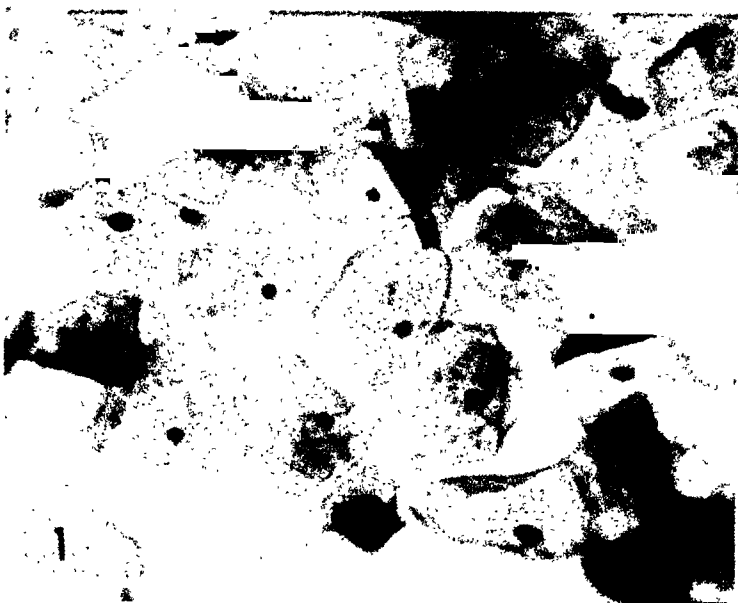


Fig. 1.—Estrogenic peak at end of follicle ripening phase. Uniformity and well-preserved state of cells desquamated during physiological activity.

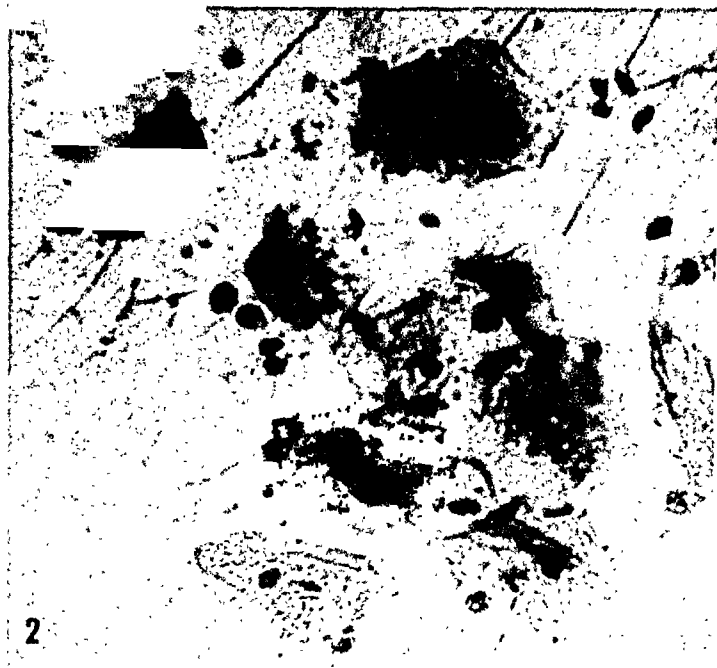


Fig. 2.—Cornified cells after estrogenic peak has passed; no luteinization; show effects of stagnant secretions before exfoliation due to absence of hormonal effects.

arrested or retarded cyclic changes were obvious; negative pregnancies could be definitely established, the positives were still doubtful; (2) the missed period at any ovarian age might be a freak reaction and followed by the normal follicle ripening of a new cycle; (3) a missed period may be caused by a previously delayed follicle ripening or a prolonged transitional phase (excessive estrogenic elaboration); (4) missed or delayed periods may be part of the general regressive signs of ovarian deficiency as found in hypopituitarism, etc.

These observations were hardly satisfactory in the materialization of the "hunch." One by one, groups of cells or individual forms were selected as possible pathognomonic features of pregnancy. The previously described "pregnancy cells" were not discovered in early cases.

All the physiological factors concerned with pregnancy were reviewed. The life of the corpus luteum begins after ovulation. How it affects the vaginal epithelium during the phase of follicle transition, and after, was the starting point.<sup>4</sup> The functionalis cells are produced in response to corpus luteum stimulation.<sup>1, 4</sup> Unlike the cornified cells found at the estrogenic peak, they are smaller, round or oval, their nuclei larger and characteristically vesicular. The follicle transition phase, not too sharply defined by time or cellular differentiation, may be considered a poised state awaiting hormonal factors to develop. Let us assume that the luteal phase has developed vigorously. Functional cells appear in great number while cornified cells diminish rapidly, those remaining showing signs of deterioration. Let us now imagine a single moment of arrested activity, i.e., a moment during which the superficial cells of the vaginal epithelium receive no stimulation from the ovary. Instead of cells being desquamated as a result of proliferation from the deeper layers, they remain in vivo in a static phase, subjected to the effects of stagnant secretions and/or other physical effects. They become frayed, shrunken, their cytoplasm full of debris. By the time they exfoliate, their appearance is altered. The same cell, desquamated during a period of activity, appears fresh and well preserved. This applies to surface cells of any tissue. *This differentiation of cells desquamated while actively influenced by physiological activity and cells shed during periods of retardation or low levels of activity (involution)*, I believe to be the most important clue in the detection of pregnancy in the vaginal smears (Figs. 1 and 2).

The peak of function of the menstrual corpus luteum is usually passed by the tenth day after ovulation.<sup>5</sup> As the corpus luteum begins to wane, the functionalis cells, which had been increasing in great numbers and appearing as fresh, vital, well-preserved cells, begin to be irregularly affected. At about the twenty-fourth day, they show signs of deterioration. Twisting, folding, cytoplasm filled with debris, they mass in clumps. The limit of growth and stratification has been reached. Superficial cells bereft of forces which have influenced their activity are now subjected to surface irritation before denudation.

The various premenstrual smears of the normal cycle reveal progressively poorer functionalis cells; debris, leucocytes, and bacteria mount; clumps

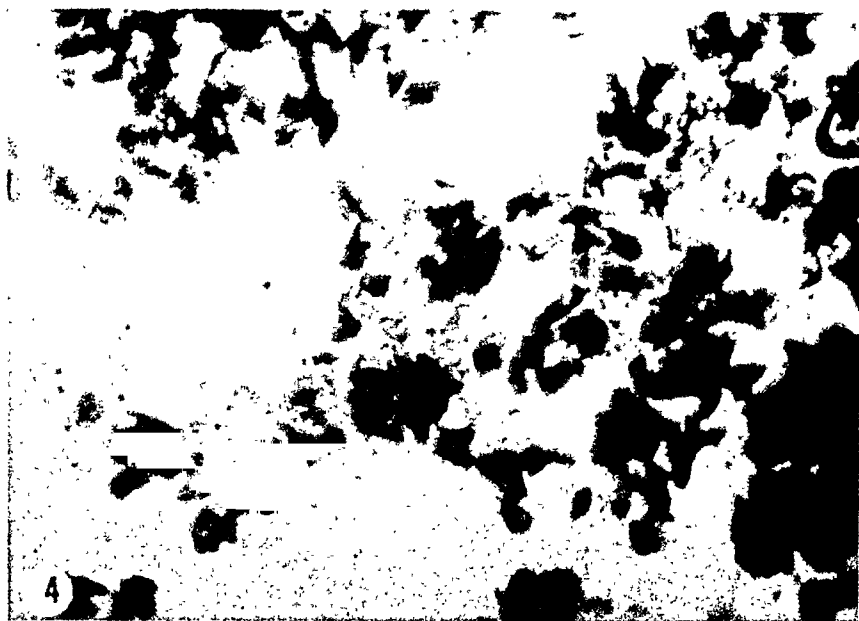


Fig. 4.—Well-established phase of luteinization: last menstrual period March 17, 1916; smear taken March 30; note loss of identity of cells near or within clumps. Twisted, deteriorating cornified cells can be detected.

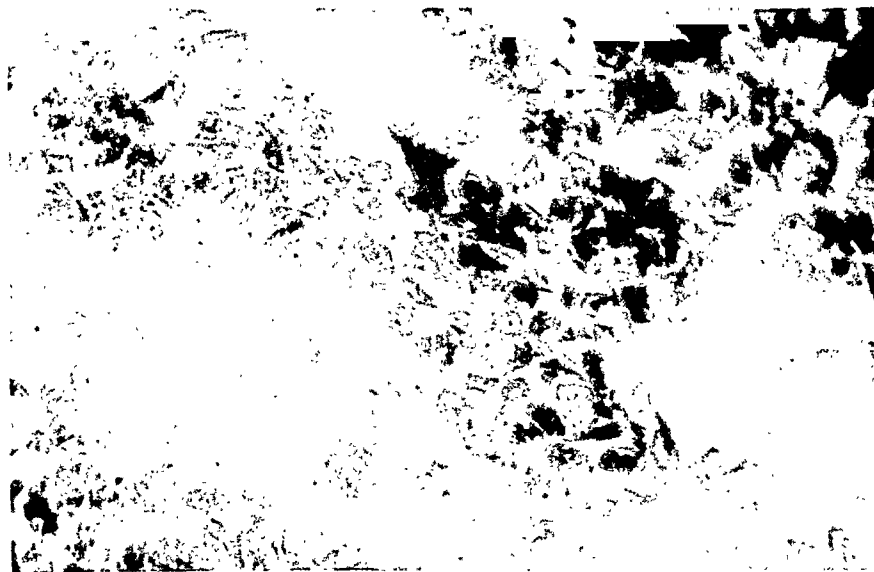


Fig. 5.—Pregnancy smear: same patient as in Fig. 4; smear taken April 4, five days later, nineteenth day of cycle. Note increase in number of functionalis cells, the well-preserved state in and near the clumps, and the absence of other than well-preserved cornified cells. They can be identified by their polygonal shapes. Child born at term, Jan. 11, 1917.

become heavier; and deterioration of the cornified cells is complete. Only remnants of their original forms are seen and recognized because of their original "red" stain. The functionalis cells which can be seen outside of the clumps have poor cellular membranes presumed there only because they limit the intracellular contents.

The above observations were obvious findings considered in the study of vaginal smears in general. Their importance in the diagnosis of pregnancy was not recognized at once.

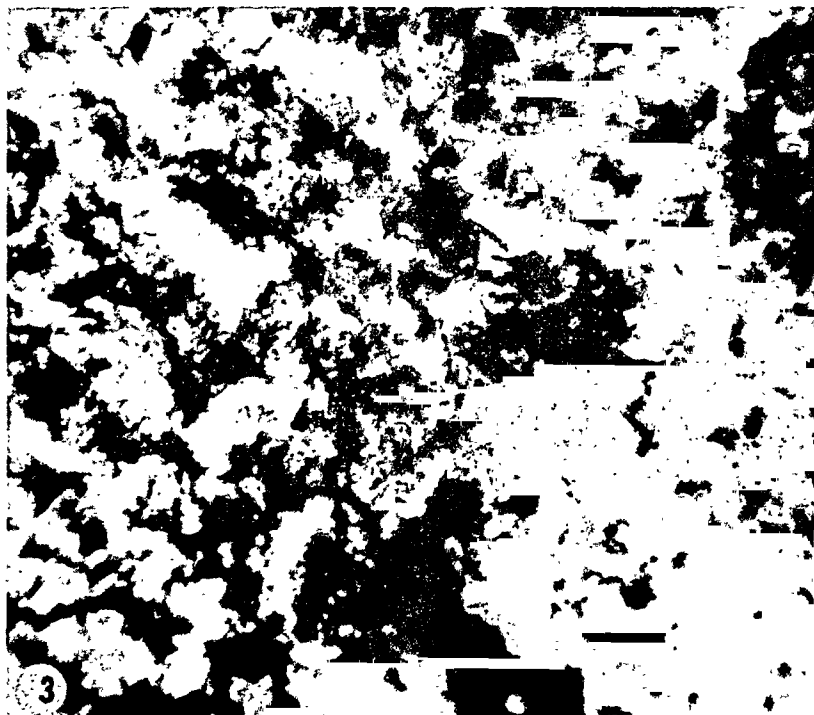


Fig. 3.—Premenstrual smear: note absence of cellular morphology. This black and white print was made from colored transparency which reveals broken, twisted fragments of cornified red cells.

In the event that conception takes place progesterational activity continues with no interruption. In fact, a surging influence toward growth and stratification results. The functionalis cells increase in even greater numbers, not a too obvious change; clumping is thinner, also not a very obvious change. The functionalis cells *retain* their freshness, the clarity of their cell membranes and cytoplasm, and the identity of their well-preserved nuclei. These characteristics are obvious especially when comparisons are made to smears of the same phase in the normal cycle. The cornified cells, though relatively few in number, too, remain well defined and well preserved, their nuclei perhaps a little larger than those of their predecessors (Figs. 3, 4, and 5).

I found most of the "typical" pregnant smears immediately after conception (Figs. 5 and 6). The rapidly produced functionalis cells are less affected during the early stages when hypersecretion of mucus and excessive debris are less prominent. The differentiating point in doubtful smears depends



twisted and folded beyond recognition except for its red color. In the pregnant smear they are in fairly good morphological state (Fig. 7).

No uniformity will be found in a series of pregnancy smears. Cells are not uniformly shed nor are they uniformly affected by the stagnant secretions. The vagina is not regularly swept clean of its contents and with physical factors such as sexual excitation, douching, and infections an otherwise typical picture is altered.

Tracing of vaginal smears throughout the entire period of gestation is not pertinent to the object of this preliminary report of a means of diagnosing early pregnancy. The corpus luteum of pregnancy remains active for one hundred twenty days.<sup>5</sup> The growth of the vaginal epithelium reaches a peak. At that time, it seems that the balance of growth and desquamation leans toward involution. The cells remain *in vivo* longer and therefore some reveal a "thickening" of their surface membranes. These are the so-called pregnancy cells, cells which are more easily found toward the end of the first trimester and later. No other apparent changes take place except those which may be attributed to physical disturbances. After the seventh month, the smears seem to clear up and appear "cleaner." This may be attributed to a decreased sexual activity.

### Discussion

The study of vaginal smears in early pregnancy was premised upon a thorough review of the hormonal influences involved. The conclusions drawn were based upon clinical application of these principles to vaginal smears as they appear in the normal sexual cycle<sup>4</sup> and in the various states of ovarian development.<sup>6</sup> Actual experiences with cases in sufficient number left much to be desired on account of the difficulty in obtaining very early smears. Many specimens were found long after delivery of full-term infants and were discovered by accident while reviewing smears for demonstration purposes.

It has been suggested that smears may be an aid in the diagnosis of pregnancy disturbances. It is reported that a high degree of cornification is a danger signal when associated with hyperemesis, and that deficiency of cornification is associated with severe toxemia and eclampsia.<sup>7</sup> Another report suggests that high therapeutic dosages of estrogenic hormones react very favorably in threatened abortions.<sup>8</sup> In analyzing these hormonal factors, it must be borne in mind that cornification, an estrogenic effect, can hardly be expected in the presence of corpus luteum or deep layers of functionalis cells.

### Conclusion

There are definite cellular patterns which can be found and recognized in the vaginal smears immediately after conception. It is firmly believed that they evidence pregnancy and can be detected before the first amenorrheic episode. The interpretation of these findings was based upon the same principles which explain all of the physiological interrelationships which take place in the female sexual tract during its development and in the normal sexual cycle of maturity.

upon a determination as to whether the corpus luteum is involuting or whether it is becoming more dominant. In one case the superficial cells of the vaginal epithelium are left to the physical effects of the surrounding media revealed by the resulting deteriorating effects. In the other case, they are desquamated in



Fig. 6.—Pregnancy smear: ten days after conception; black and white print made from colored transparency. Red cornified cells (arrows) in this field 15 per cent, the others are blue functionalis cells.

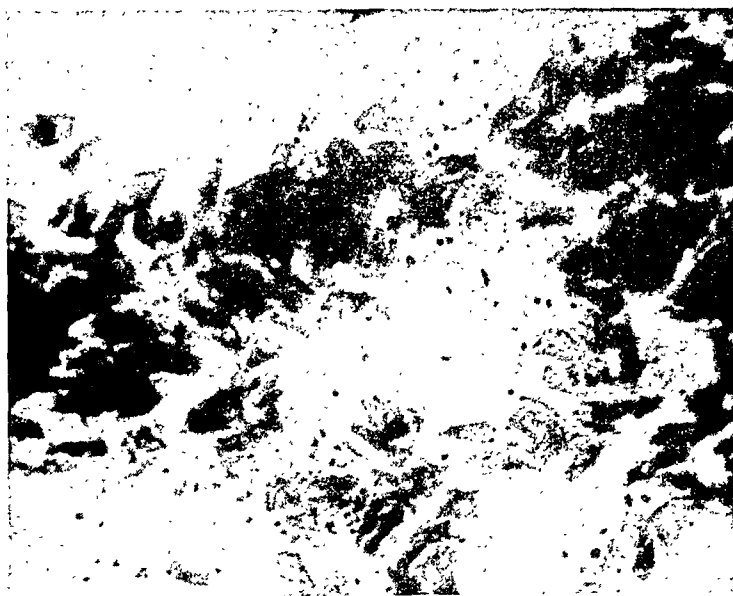


Fig. 7.—Pregnancy smear: six weeks after last menstrual period. Note cells within and about the clumps; they are well defined and have clear cellular membranes (Compare with Fig. 4).

a well-preserved state. The nonpregnant premenstrual smear is thickly clumped, the functionalis cells poorly preserved. The pregnant smears are thinner and fairly well clumped. But in spite of this, by careful focusing, the identity of the cells can be recognized. The cornified cell in the nonpregnant smear is

## SPECIFIC MALIGNANT CELLS EXFOLIATED FROM PREINVASIVE CANCER OF THE CERVIX UTERI\*

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THE diagnosis of cancer of the cervix in its preinvasive phase constitutes one of the greatest challenges to the medical profession. Cure is certain if the abnormal growth is removed before invasion has occurred.<sup>1</sup> While it is impracticable to subject every woman above a certain age to diagnostic surgical procedures, screening for possible cancer can easily be accomplished by the use of the endocervical smear technique. Unless otherwise indicated, diagnostic surgical procedures can be limited to those patients in whom suspicious cells are found in the smear.

### Procedure and Results

On routine investigation of 3,700 women of all social strata, twenty-two cases of preinvasive cancer of the cervix and four borderline cases were discovered by means of the endocervical smear technique. The diagnosis was made from biopsies or from endocervical curettage. To obtain material for the smear, an ordinary cotton applicator is inserted about one-half to three-fourths inch into the cervical canal, twirled a few times around and against the squamocolumnar junction. The material is spread evenly on a slide which is then fixed immediately in a solution of equal parts of ether and 95 per cent alcohol and stained by the method of Papanicolaou.<sup>2</sup> Confirmation of a positive smear is always sought by a diagnostic curettage, cervical biopsy, and endocervical curettage.

After detecting the first ten cases of preinvasive cancer, it was noted that the exfoliated cells in smears from preinvasive cancers differ greatly from those of invasive cancer. An attempt has been made actually to distinguish between the exfoliated cells from preinvasive cancer and those from invasive cancers by the difference in cell morphology. In eight of the last twelve cases of preinvasive carcinomas, the diagnosis was suspected from a study of the endocervical smear. All smears from patients with preinvasive carcinoma have been reviewed and in only three out of the total of twenty-two cases was there an absence of the "specific" cells.†

The morphology of exfoliated cells from a preinvasive cancer is extremely diverse and can be distinguished from invasive cancer cells and atypical cells in conditions other than cancer solely by comparison. The main characteristics and distinguishing features of preinvasive cancer cells are the following: They are usually larger than invasive cancer cells and have a greater amount of cytoplasm which usually stains a typical orange-yellow. The nuclei may be either small, hyperchromatic without details, and the nuclear membrane may be very

\*Aided by a grant from the American Cancer Society.

†By the screening of a further group of women, twelve patients with preinvasive carcinoma were found. In eleven of these cases the exfoliated cells were those of the preinvasive type, and the diagnosis was made accordingly.

There is still necessity for a great deal of additional observation. Of utmost importance is the question of a persistent corpus luteum. With the accumulation of additional data from many sources, its significance will be given its proper place in these considerations.

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Once the characteristic features of the exfoliated cells are understood, it is relatively easy to distinguish the exfoliated cells of preinvasive cancer from those of invasive cancer. Some difficulty may be encountered, however, in the differentiation of these cells from the atypical cells found in inflammation. When atypical cervical cells are formed and exfoliated as a result of inflammation, they are usually found in large numbers, form adherent clusters and have less cytoplasm than the exfoliated preinvasive cancer cells. Inflammatory cells are more uniform in size and have none of the features described for preinvasive malignant cells.

Fig. 3.



Fig. 4.

Fig. 3.—Endocervical smear. Note large foamy agranular nuclei with much cytoplasm and two hyperchromatic nuclei.

Fig. 4.—Microscopic section; biopsy of cervix, same patient as Fig. 3. Occasional foci of preinvasive carcinoma in mouths of the glands.

### Conclusions

Recognition of the specific characteristics of the exfoliated cells of preinvasive cancer may in the future contribute to the detection of a greater number

irregular (Fig. 1), or they may be large, foamy and agranular with well- or ill-defined borders (Figs. 3 and 5). On the other hand, nuclei may be found with distinct borders and a particular type of granularity which is never found with invasive cancer (Fig. 7). Bizarre forms, multinucleated or multinucleated giant cells characteristic of invasive cancer, are rarely found in smears when the cancer is in the preinvasive phase. Exfoliated cells from a preinvasive cancer generally

Fig. 1.

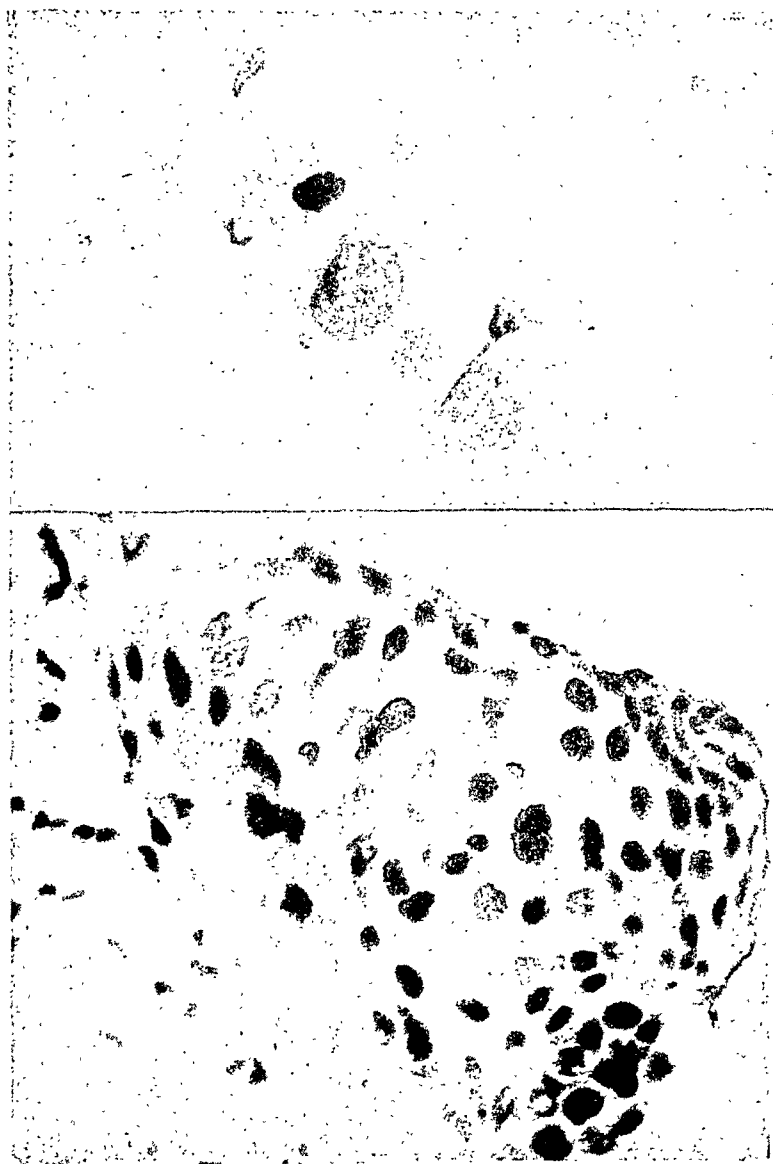


Fig. 2.

Fig. 1.—Endocervical smear. Note small hyperchromatic nucleus with irregular border and two cells with large foamy nuclei. The cytoplasm has an orange-red color.

Fig. 2.—Microscopic section of endocervix; same patient as Fig. 1. In one fragment a minute group of anaplastic squamous cells lying in a cleft.

appear singly or in loose groups but never in adherent clusters. In addition, there is usually a striking predominance of normal cells and the cells in the smears from the vaginal pool may be completely cornified although the patient may be in the luteal phase of the menstrual cycle or of postmenopausal age.

### Summary

The finding of a specific type of exfoliated malignant cells from preinvasive cancer is described and the morphology discussed.

In thirty of thirty-four cases of preinvasive cancer these specific cells were found, and in nineteen of twenty-one cases the diagnosis of preinvasive cancer was actually suspected and confirmed by biopsy.

FIG. 7.

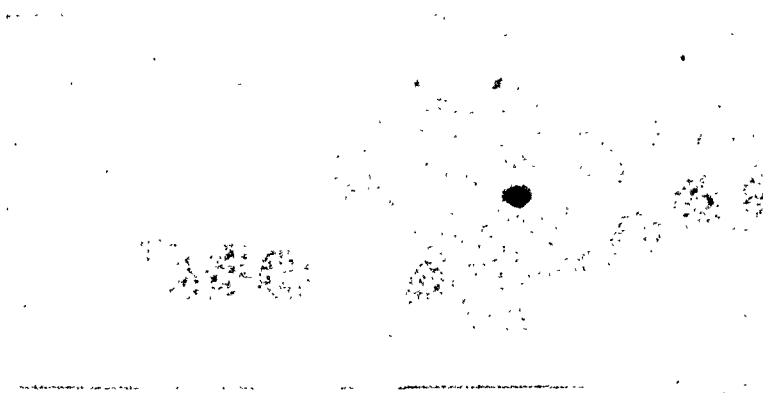


FIG. 8.

Fig. 7.—Endocervical smear. Note cancer cells with a particularly marked even granularity. The large cell in the center is a cornified cell.

Fig. 8.—Microscopic section; same patient as Fig. 7. Preinvasive squamous cell carcinoma in five of six sections of cervix obtained at hysterectomy.

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of curable cases of cancer. Invasive cancer is usually comparatively easily confirmed by a single biopsy, however, pre-invasive cancer may frequently be missed by one or more biopsies. The knowledge that the case under investigation is probably one of preinvasive cancer may prevent discarding a slide as a false positive in the presence of a first or second negative biopsy. This is important in view of the recent findings of Pund and Auerbach<sup>3</sup> that 3.9 per cent of 1,200

Fig. 5.

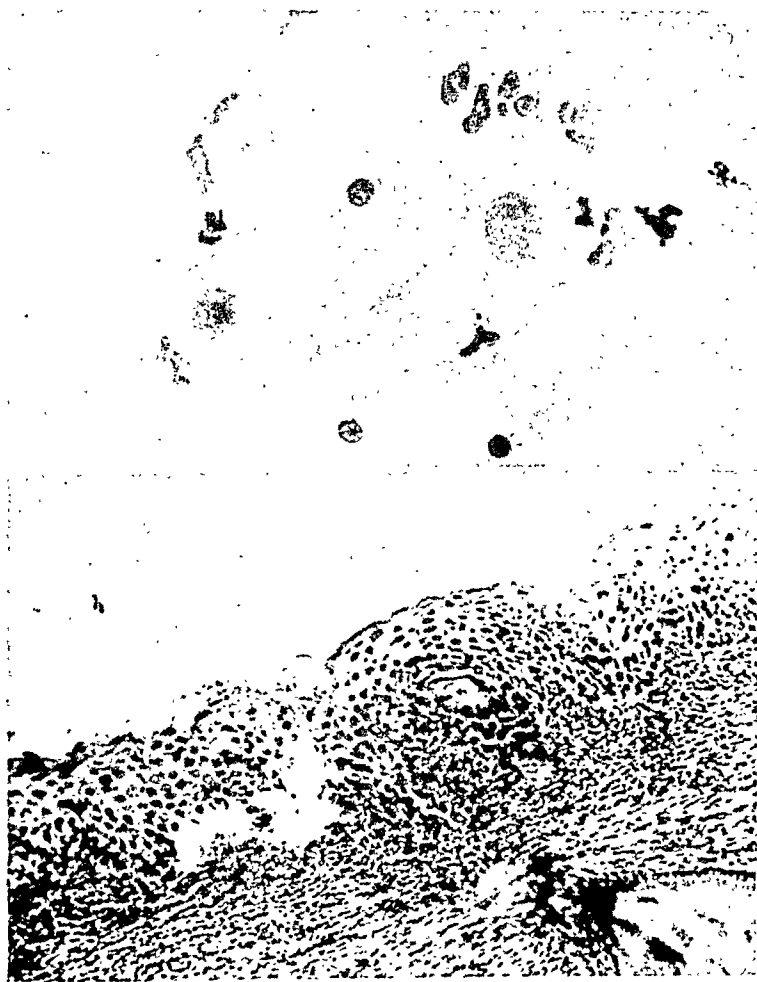


Fig. 6.

Fig. 5.—Endocervical smear. Note three normal cornified cells and two malignant cells one of which has a nucleus with ill-defined borders.

Fig. 6.—Microscopic section; same patient as Fig. 5. Preinvasive squamous-cell carcinoma of only one of numerous small sections of cervix obtained at biopsy.

cervices obtained by hysterectomy showed preinvasive cancer and that the average age of the patients was 36.6 years, the youngest being 23 and the oldest 53. Furthermore, it appeared that the transition from the preinvasive to the invasive phase may require an average of six years and that the appearance of clinical signs may be delayed an additional six years. Thus routine screening of all women by the endocervical smear technique should constitute an important part of preventive oncology.



Fig. 1.

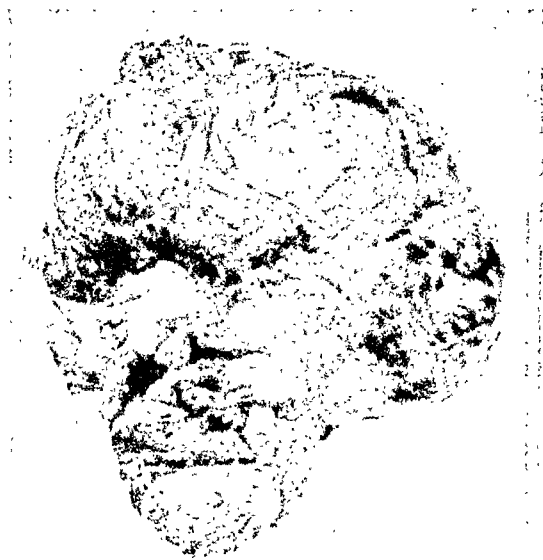


Fig. 2.

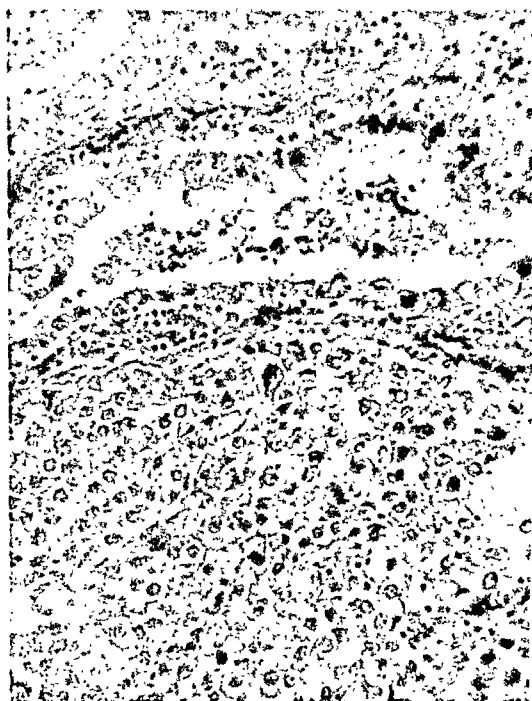
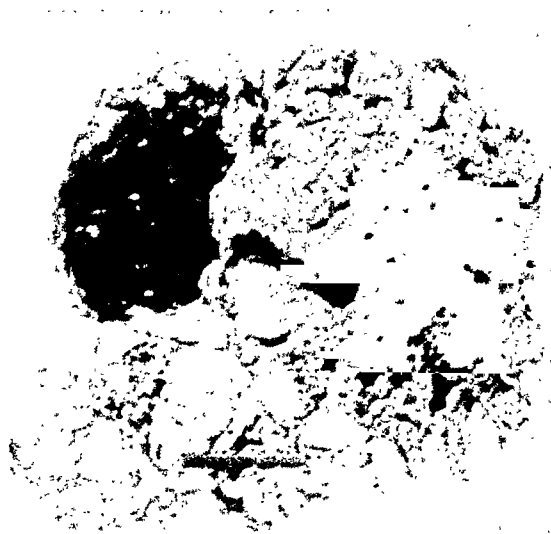


Fig. 3.

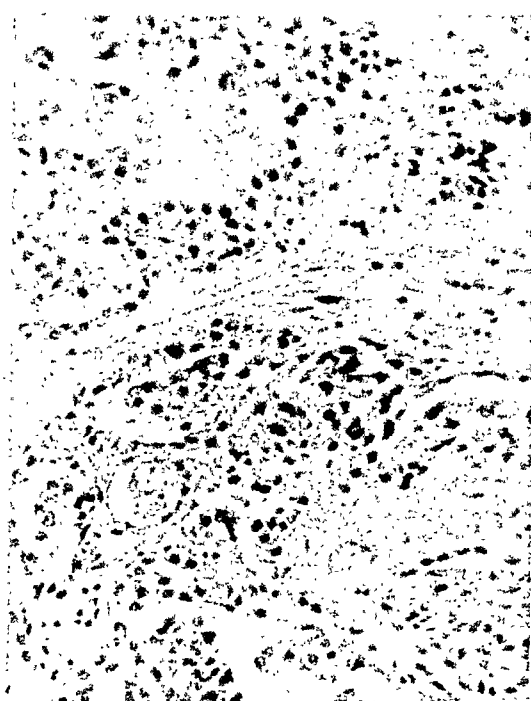


Fig. 4.

Fig. 1.—External view of uterus, tubes and left ovarian tumor. Ovarian tumor mass measured 20 by 19 by 9 cm., weighed 2,204 Gm.

Fig. 2.—Cut section of tumor showing yellow-orange nodules of varying size and multiple cystic spaces filled with bright red hemorrhagic material.

Fig. 3.—Photomicrograph of large clear cells arranged in solid nests. ( $\times 220$ )

Fig. 4.—Photomicrograph showing multiple cystic spaces lined by moderately large, clear cells showing papillary projections. ( $\times 220$ )

## PAPILLARY CLEAR CELL ADENOCARCINOMA OF THE OVARY

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SINCE Schiller<sup>1</sup> first described mesonephroma ovarii in 1939, 46 cases have been reported in the literature, to our knowledge, and Schiller states that he has seen an additional 33 cases, making a total of 79.

The tumors are not characteristic grossly and vary from solid to cystic and papillary. Clinically, they produce no characteristic symptoms other than those which can be attributed to an abdominal mass. There is no abnormal uterine bleeding or evidence of any hormonal secretion or secondary sex changes. The age incidence in the reported cases has varied from 8 months to 72 years but generally they are seen past the age of 50. They may be benign or malignant.

We present two additional cases.

CASE 1.—Mrs. R. D., 65-year-old white woman, was admitted to the North Side Unit of the Youngstown Hospital Association March 13, 1948, complaining of gradual enlargement of the abdomen and generalized abdominal pain of six weeks' duration. She had lost 35 pounds in the past year. Her bowels had been irregular and frequent cathartics had been required. She had vaginal bleeding for four and one-half months, about fifteen years ago. She received x-ray therapy and she had had no vaginal bleeding or menstrual periods since.

Physical examination showed a markedly emaciated woman with a noticeable brownish pigmentation of the skin. No secondary sex characteristics were noted. The abdomen showed a fixed, tense, cystic, irregular mass which filled the pelvis, extended laterally into both flanks and superiorly to slightly above the umbilicus. Vaginal examination showed the cervix displaced high and anteriorly under the symphysis. At operation, on March 17, a large semisolid pelvic tumor mass occupying the area described above was found almost completely fixed on the left side. The omental vessels adherent to the tumor were markedly distended. The uterus, right tube, and ovary were small and atrophic. A bilateral salpingo-oophorectomy and panhysterectomy were done.

*Gross Pathology.*—The large tumor mass measured 20 by 19 by 9 cm., weighed 2,204 Gm., was nodular, yellow-orange, and was covered by a tough, white fibrous capsule (Figs. 1 and 2). It was semisolid to palpation. On section, it was composed of friable, yellow-orange nodules varying in size, with large cystic spaces measuring up to 8.5 cm. in diameter which were filled with bright red hemorrhagic clotted material.

*Microscopic Findings.*—The uterus, tubes, and right ovary are not remarkable. The sections from the left ovarian tumor show fairly uniform, cuboidal, moderately large cells with pale cytoplasm, sharply defined cell borders, moderately large nuclei with clumping of the chromatin. Nucleoli are especially prominent. The cells are arranged in sheets or nests (Fig. 3) but in many places line cystic spaces. Most of the cystic spaces have papillary projections covered by similar cells. In some of the larger cystic spaces, three or four papillary projections are seen, while others contain but one (Fig. 4). Some of the lumina contain exfoliated tumor cells, and cellular debris. The cells found in the solid nest are larger and of more irregular shape. Vascularization is prominent. Many large sinusoids are lined by tumor cells and filled with well-preserved blood. Necrosis and hemorrhage are prominent throughout the tumor and there is an associated lymphocytic and mononuclear cell infiltration

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The patient's postoperative course was uneventful and she was discharged on May 4, her tenth postoperative hospital day. One month after surgery the patient had no specific complaints. Pelvic examination showed no induration or masses. The patient is receiving x-ray therapy.

Fig. 5.

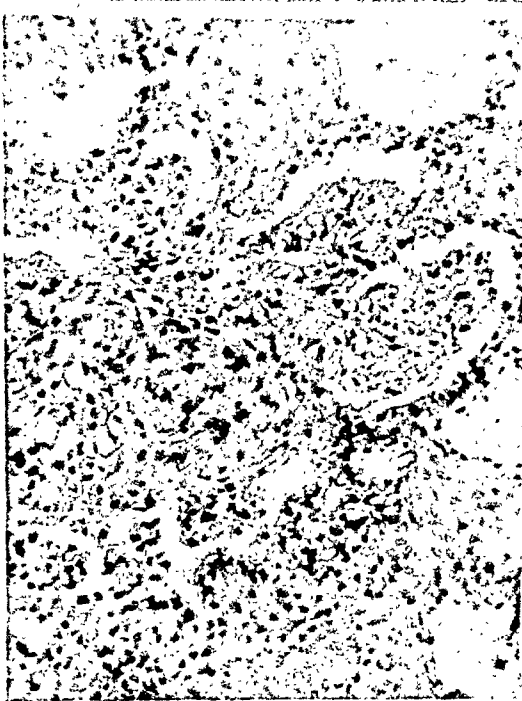


Fig. 6

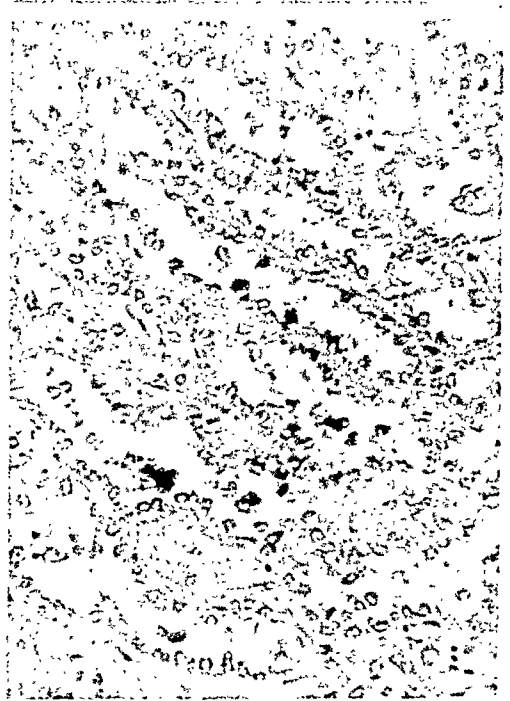


Fig. 7.

Fig. 5.—External view of uterus, both tubes and left ovary. Cut section of the right ovarian cystic mass showing the multiple yellow, polypoid projections.

Fig. 6.—Photomicrograph showing multiple cystic spaces lined by moderately large clear cells with prominent and projecting nuclei. Papillary projections covered by similar cells are seen within the lumina. (X155)

Fig. 7.—Photomicrograph showing the tubule-like structure lined by cells with basophilic and granular cytoplasm. (X220)

### Discussion

The varied terminology used to describe this tumor in the literature has depended upon the author's viewpoint. The gynecologist, who desires a classifi-

throughout the stroma. Masson's trichrome and Wilder's reticulum stains show a delicate reticular stroma. Mucicarmine stain fails to reveal mucin. Sudan IV stain shows most of the cells to contain small globules of fat. Abundant fat, however, is associated with the areas of severe necrosis.

The patient's postoperative course was uneventful. X-ray therapy was started six days after surgery and a full course was given. On follow-up six weeks postoperatively, no masses or tenderness were found. There was an area of ulceration in the left lateral vaginal wall which was thought to represent radiation necrosis. Papanicolaou stained vaginal smears were negative for tumor cells. Three months postoperatively this ulcerated area had regressed. The patient had no complaint and had gained 10 pounds in weight.

CASE 2.\*—Mrs. S. W., 58-year-old white woman, was admitted to the North Side Unit of the Youngstown Hospital Association April 22, 1948, stating that she had noticed enlargement in the lower abdomen for eight months, which had become more marked in the last two months. She had had several episodes of "cystitis" characterized by frequency and burning. The burning cleared with "sulfa" drug but the frequency remained. For this reason she consulted a urologist who found a pelvic tumor. She denied any weight loss and stated her general health had been good. The past history was not pertinent. Her menstrual periods were formerly regular but she had not menstruated for 2 to 3 years.

Physical examination of the abdomen showed a large, fairly firm mass about the size of a grapefruit in the lower mid-abdomen. The mass was movable and slightly tender. No other organs were palpable. Pelvic examination revealed the cystic mass to be in the right adnexa. No secondary sex characteristics were noted. On April 24, under cyclopropane-curare anesthesia, a low midline incision was made. On opening the peritoneal cavity a large, deep purple, right ovarian mass was found. It was adherent to the right side of the pelvis and displaced the uterus against the bladder. The right tube was dilated. Bilateral salpingo-oophorectomy, hysterectomy, and appendectomy were done.

*Gross Description.*—The uterus, left tube, and ovary were essentially negative. The right tube measures 7 cm. in length and up to 8 mm. in diameter. The frimbriated end was bound densely to the large ovarian tumor and there was a small amount of red-brown material in the lumen. The right ovarian cystic mass measured about 22 cm. in its greatest diameter (Fig. 5). The external surface was blue-gray and smooth. It was filled with a thin, brown fluid. Arising from the inner wall of the cyst were numerous soft, yellow, polypoid projections, the largest of which measured 4 cm. in diameter.

*Microscopic Findings.*—The tumor shows numerous cystic spaces lined by low cuboidal epithelium with prominent and projecting nuclei. Nucleoli are inconspicuous. The nuclei show well-defined borders with irregularly clumped chromatin. The cell border is generally distinct, the cytoplasm clear and occasionally somewhat foamy. Many of the cysts are filled with pale pink, granular material which does not prove to be mucin on special staining. In other areas, the tumor shows solid nests of similar, although larger, cells. In other areas there are papillary projections into the lumina (Fig. 6). Here, the cytoplasm of the cell is basophilic and granular, while other places are covered by the same type of cells that lines the cystic spaces. Vascularization of these papillary projections is prominent. Sinusoids lined by tumor cells and filled with well-preserved red blood cells are seen. Necrosis is prominent throughout. Sudan IV stain shows small globules of fat in macrophagic cells in the interstitial tissues, and in many of the cells lining the cystic spaces. Fat is more prominent and found in larger globules in the areas associated with necrosis. Some areas demonstrate tubular structures lined by cells possessing basophilic and granular cytoplasm (Fig. 7). Masson's trichrome and Wilder's reticulum stains show scanty, loosely arranged, interstitial tissue with moderate vascularization. The right tube exhibits scarring of the plicated mucosa and wall. Some plicae are absent but the epithelium is uniform. Within the lumen in some zones one sees large numbers of very pleomorphic swollen cells with clear cytoplasm and dense hyperchromatic small nuclei.

\*Acknowledgment is made to Dr. G. G. Nelson for this case.

Kazaneigil and co-workers<sup>8</sup> preferred to classify these tumors as papillo-endotheliomas. These authors felt that there was a definite endothelial character in the arrangement of the tumor cells, which assumed an angiomatous and cavernomatous appearance in one of their cases, and an angio-endotheliomatous picture in another case with foci of hematopoiesis. This, they thought, might indicate a primitive angioblastic mesenchymal reaction.

Saphir and Lockner,<sup>9</sup> on the basis of two cases examined, leaned toward Schiller's conception in order to explain the origin of these tumors. However, as a pathologist, he proposes a purely descriptive anatomical diagnosis of adenocarcinoma with clear cells (hypernephroid) of the ovary which implies that this is synonymous with mesonephroma.

Jones and Seegar<sup>10</sup> report six cases in a paper entitled "Mesonephroma of the Ovary." Their conclusions hardly support the validity of this title, inasmuch as they believe that true glomeruli were not present. In a later paper,<sup>10</sup> these authors were not able to supply any further data which might elucidate this question, thus leaving the origin unsettled.

In attempting to establish a histiogenetic classification of ovarian tumors, Spencer and Reel<sup>11</sup> considered the possibility of mesonephroma. This is on theoretic ground and they offer no conclusive proof other than Schiller's work to support this contention.

Schiller<sup>12</sup> has stated that he had never seen a primary carcinoma of the ovary, but that they always arose in benign tumors. The origin of one of our tumors could have been in a papillary cystadenoma of the ovary. We would disagree with Stromme and Traut<sup>4</sup> who state that their tumors produced mucin and for this reason would not consider a serous cystadenoma origin. In contrast to their cases, our tumors failed to show mucin. We would agree with Stromme, however, that probably these tumors are not as clearly defined a group as was originally outlined by Schiller.

That these tumors are mesonephric in origin has been accepted by several authors, and such a terminology has been used by the Ovarian Tumor Registry.<sup>12</sup> While this approach is commendable, for we must begin to classify tumors on an embryologic basis, the acceptance of this concept, we believe, has occurred on scanty proof. Although our cases do not exactly fit Schiller's original description, we do feel they are similar. The two tumors did show epithelium which resembled that described by Schiller in his original work. However, we did not demonstrate mesonephric glomeruli. The papillary projections into the cystic spaces contain capillaries but the resemblance to glomeruli is difficult to recognize. In many cystic spaces there were three or four papillary projections and a few cystic spaces were seen which had only one. One should expect papillary projections into cystic spaces in a rapidly growing neoplasm. In malignant tumors, however, one should not expect an exact reproduction of a structure as complex as a glomerulus since dedifferentiation is a feature of neoplasms.

Novak,<sup>5</sup> who examined slides from our two cases, states he feels Schiller's mesonephroma often represents only a variant of adenocarcinoma. In both our cases, he felt the prevailing picture was that of a clear-cell adenocarcinoma.

The proof of the glomerular nature of these papillary projections, we believe, should depend upon very definite anatomic criteria. A well-formed Bowman's capsule should be identified. The glomerular tufts should be distinct with well-formed capillaries lined by endothelium and with a definite basement membrane and a tubular connection to the glomerulus should be found. Equally important, their functional nature should be ascertained. In reviewing the literature, we have been unable to find satisfactory proof of any of these morphologic criteria. No comment has been made, to our knowledge, of physiologic activity of these glomeruli. If we assume them to be true glomeruli, certainly

cation based on physiology and endocrinology, classifies it as a virilizing or non-virilizing lipoid cell tumor.<sup>2</sup> The embryologist classifies it as mesonephroma<sup>1, 3</sup> or a teratoid adenocystoma.<sup>4</sup> The morphologist classifies it as a papillary clear-cell adenocarcinoma.<sup>5</sup> The oncologist classifies it as a hypernephroid tumor.<sup>6</sup> We have no objections to the varied terminology applied, but we feel that the most important approach would be based upon the determination of the basic substrate from which the tumor arose.

Barzilai,<sup>2</sup> who has established a very satisfactory classification for ovarian tumors, has deviated from her original concept of relating the tumor to a specific cell origin and has thrown haphazardly into a single large category many tumors solely on a virilizing characteristic. This is of no value in classification but tends to confuse the issue, inasmuch as she includes such terms as hypernephroma, hypernephroid tumor of the ovary, adrenal tumor of the ovary, luteinoma, interstitioma and masculinovoblastoma under a single heading. She does, however, believe in an additional group separate from the above to which she has given the name mesonephroma in agreement with Schiller.

Stromme and Traut<sup>4</sup> believe that these tumors in question represent a teratoid adenocystoma and only in well-differentiated types are tumors seen which simulate the morphology of Schiller. These authors were likewise unable to demonstrate structures acceptable as glomeruli although papillary structures were abundantly present.

Schiller,<sup>1, 3</sup> in 1939, separated from a group of papillary ovarian tumors a group to which he gave the name mesonephroma ovarii, because, histologically, he felt these tumors were sufficiently different to justify a separate grouping. They possessed an epithelium which was generally flat, irregular with wavy lines, prominent projecting nuclei and thin rims of cytoplasm giving it a so-called button or hobnail-like appearance. The tumors are generally cystic with a tendency toward papillary projections into the lumina. The cells lining these spaces appear to resemble endothelium but where active proliferation was evident, it approached an epithelial form. These papillary projections possessed two or at most three capillary tufts and resembled the glomerulus of the mesonephric kidney.

Embryologically, the gonad is closely related to the mesonephric kidney and the adrenal gland. They are separated by the formation of the genital groove and separation is complete when the ovarian ligament is developed. Should the genital groove occur more peripherally, it is possible that some mesonephric elements might be included in the ovary. Inclusion of other tissues within the hilus of the ovary is known to occur. Islands of adrenal rests are recognized and Geist showed that after bilateral adrenalectomy a proliferation of these cells occurred in animals which survived. The reporting of these tumors in the testis, kidney, ovarian ligament, and associated with other ovarian tumors such as dermoid and embryoma would definitely suggest a disturbance in the usual embryological mechanisms.

We feel that the mesonephric origin of these tumors can be questioned. The true Wolffian duct tumors<sup>7</sup> are generally retroperitoneal or intramesenteric and these tumors show glomeruli and tubules. In the mesonephroma, the glomerular structures are generally scarce and poorly developed and tubules are absent. Schiller,<sup>1</sup> by preparing serial reproductions of these papillary structures, felt that he definitely proved their glomerular nature. Kazancigil and co-workers,<sup>8</sup> however, attempted to reproduce Schiller's work but were unsuccessful. The variation seen in the epithelium from flat to cuboidal or low columnar is the picture seen in the mesonephric glomerulus, however. Tubules in these tumors are rare. Why they are not found has never been satisfactorily explained. Schiller suggests that the rarity may be due to the fact that the Wolffian duct is not close enough to stimulate tubule formation.

## THE "CRUSH" SYNDROME IN OBSTETRICS AND GYNECOLOGY\*

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THE crush syndrome is part of a general syndrome of urinary suppression and azotemia; it is not caused by kidney disease and, therefore, is of extra-renal origin.

This general syndrome has been designated as lower nephron nephrosis by Lucke<sup>1</sup> and as acute tubular disease and acute toxic nephrosis by Moon.<sup>2</sup> It follows a variety of causes of which the following have been noted: shock (either traumatic or operative), transfusion reactions, burns, medical diseases associated with dehydration or marked hypotension, such as is found in severe infections or at the end of a chronic debilitating disease, toxic poisoning, and heat stroke.

A complete review of the literature will be found in studies by Lucke,<sup>1</sup> Moon,<sup>2</sup> Martineau and Hartman,<sup>3</sup> Corcoran and Page,<sup>4</sup> and Bell and Knutson.<sup>5</sup>

The crush syndrome refers specifically to posttraumatic anuria and consists of the initial tissue damage or injury followed by shock which may be severe, moderate, or at times absent; then sudden urinary suppression. That urine which is passed is scanty, acid, of low specific gravity, colored red or brown with myoglobin, and contains pigmented casts, leucocytes, and albumin. Meanwhile, azotemia appears, as shown by increasing blood urea nitrogen; the patient becomes restless, with thirst and vomiting, and between the fifth and ninth days dies or starts to recover spontaneously. If recovery ensues there is apparently no permanent renal damage.

### Pathology

There are two groups or related states of renal injury: first, those in which the principal lesion is the obstruction of the renal tubules by pigmented (myoglobin, hemoglobin) casts; and, second, those in which the injury lies principally in necrosis of the epithelium of the distal convoluted tubules. The underlying mechanism in all these changes is not clearly understood but seems to occur in the following sequence: the initial injury causes a stimulation of the renal vasomotor nerves which in turn causes a renal ischemia by constriction of the cortical interlobular arteries and diversion of blood into the medulla. This causes oliguria and aciduria which facilitates the precipitation of pigmented casts and necrosis of the tubular epithelium. The damage to the tubular epithelium allows the urinary filtrate to be reabsorbed into the circulation by a process of diffusion. Thus, the oliguria or anuria is produced by the interruption of renal secretion.

James Young<sup>6</sup> of London first reported this syndrome in connection with obstetrical injuries and the authors,<sup>7</sup> in a previous paper, reported three cases, two of obstetrical origin and one a twisted ovarian cyst. In the present paper we have reviewed all the maternal deaths in the city of Philadelphia from Jan. 1, 1930, to Dec. 31, 1946. This material was obtained from the records of the Maternal Mortality Committee of the Philadelphia County Medical Society. From this series of fatal cases totaling 2,000 in number we found five deaths that showed the characteristic syndrome of urinary suppression following trauma. Adding these to the three cases from the previous paper, we are reporting a total of eight cases; six maternal deaths, one ruptured uterus with recovery, and one twisted, infarcted ovarian cyst with recovery.

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a uriniferous filtrate should be produced. Since excretory tubules are absent, should we not expect accumulation of the filtrate with the formation of cysts similar to the retention cyst of the adult kidney?

It does not seem wise to introduce into our thinking of ovarian tumors a concept which parallels that used in the hypernephroma of the kidney. The tremendous amount of work with the paucity of positive results in the renal tumor, should be a warning against transferring the type of reasoning originally used by Grawitz, to this ovarian tumor.

### Summary and Conclusions

1. Two yellow nonvirilizing tumors of the ovary occurring with no specific symptoms are reported.
2. One tumor was solid, the other was papillary and cystic.
3. Microscopically, they showed moderately large, clear, lipoid-containing cells arranged in solid nests and lining cystic spaces showing papillary projections.
4. The mesonephric origin of these two tumors could not be accepted as proved.

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peritoneal cavity. The patient received seven blood transfusions and had a stormy convalescence. Urinary suppression occurred the first two days and then began to improve. The blood urea nitrogen reached a maximum of 56.5 mg. per cent on the fourth day post partum but returned to normal two days later. The patient eventually recovered and was discharged on the forty-second day post partum.

**CASE 7.—Rupture of Uterus:** G. G., aged 32 years, a secundigravida, began labor at term with a breech presentation due to an unrecognized hydrocephalic monster. After twenty-four hours of difficult labor, extraction was attempted. The body was delivered but the head obstructed. Eventually the baby was delivered by craniotomy after a great deal of manipulation. Immediately following the delivery the uterus was found to be ruptured by a tear extending from the cervix to the fundus. Abdominal operation showed free blood in the peritoneum and the rent was sutured without hysterectomy. The patient received a blood transfusion. Urinary suppression with nitrogen retention developed immediately and she died on the sixth day post partum with the characteristic symptoms of lower nephron nephrosis.

**CASE 8.—Twisted Ovarian Cyst:** (Reported in previous paper.) R. Z., a woman 22 years of age, was suddenly seized with pain during a normal menstrual period. This marks the twisting of the cyst with infarction or the initial trauma. Immediately urinary suppression developed. Pain and urinary suppression persisted for four days but the patient remained at home against the advice of her physician. Finally, she was admitted to the hospital with a diagnosis of left renal calculus producing urinary obstruction with reflex anuria of opposite side. Cystoscopic studies were negative except for the passage of a little reddish-brown urine. Finally on the sixth day after the twisting of the cyst, urinary output began to increase and the patient to improve. Further studies revealed a large tumor in the abdomen, high on the left side. Operation performed twenty-six days after the original accident showed the cyst to be twisted three times on its pedicle, infarcted, with bloody extravasation into the cyst wall. The recovery was uneventful.

### Comment

All of this group of cases show the same sequence: first, trauma, either accidental or surgical, followed by urinary suppression and azotemia. It is possible that, in some cases, the syndrome may have been caused by unrecognized incompatible blood transfusion reactions; but the hospital records were studied with care and we believe that each case reported is authentic. Six of the eight cases received blood; none was given in the case of tubal abortion and multiple operations or in the case of twisted ovarian cyst.

If the treatment for shock is delayed or is inadequate the renal damage soon progresses to the degree that it cannot be controlled and the disease must run its inevitable course ending in death or recovery. It is well known that the best treatment for shock is blood transfusion, which should be given early and often. In this study, we believe that six of the eight cases were treated inadequately by transfusion: five received only one transfusion and one received none. Of the two cases with recovery, transfusion was not indicated in one (the twisted cyst) at the time of admission to the hospital, and the patient with ruptured uterus received seven transfusions, starting as soon as the rupture was discovered. The use of these transfusions early and frequently may have been the deciding factor in preventing extensive renal damage.

The treatment of "crush syndrome" begins with prevention. First: prevent obstetrical errors, chiefly birth trauma following dystocia. The two cases of ruptured uterus are examples of faulty judgment. In the first case, the error lay in failure to recognize hydrocephalus and in an improperly performed destructive operation. In the second case, the administration of pituitary extract during the first stage of labor caused a disaster that was almost fatal. Second: prevent shock or, if it occurs, treat it promptly and adequately. As was men-

## Report of Cases

CASE 1.—*Placenta Abruptio*: J. I., 40 years old and pregnant about 28 weeks, who showed mild hypertension throughout pregnancy and slight albuminuria during the preceding month, developed placenta abruptio. One hour later she was brought to the hospital and five and one-half hours later was operated upon. A typical Couvelaire uterus was found with retroplacental blood clots, infiltration of uterus and broad ligaments.

A classic cesarean section was performed and the patient was given one blood transfusion and fluids postoperatively. A typical urinary suppression followed, terminating in death on the fifth postpartum day. Autopsy showed toxic nephrosis of the kidneys with chronic glomerular nephritis and necrosis of spleen.

CASE 2.—*Placenta Abruptio*: S. M., 18 years old, a gravida i at term, developed moderate hypertension, 160/110, and albuminuria. Four days later placental separation began; first with pain and, eight hours later, bleeding. Three hours later she was admitted to the hospital in active labor and conservative treatment was administered in the form of morphine, puncture of membranes, and manual dilatation of cervix. Delivery was spontaneous about 24 hours after the onset of symptoms. The baby weighed 4,080 Gm., was full term and stillborn.

The placenta showed that two-thirds had separated prematurely. The blood loss was measured as 500 c.c. intrapartum and 350 c.c. postpartum. In addition the blood loss before admission added to the total. The patient received one transfusion of 350 c.c. post partum. Following delivery, she developed the typical symptoms of urinary suppression and azotemia and died three days post partum. Autopsy showed renal tubular necrosis and glomerular ischemia.

CASE 3.—*Placenta Abruptio*: (Reported in previous paper.) M. C., 29 years of age, gravida ii, was admitted to the hospital at 28 weeks of pregnancy for hypertensive disease and pre-eclampsia. After a week of conservative treatment placenta abruptio suddenly developed with a blood loss of about 300 c.c. and no shock. This was treated by prompt cesarean section and transfusion of 500 c.c. Immediately following operation the patient developed urinary suppression and azotemia. Urinary output began to return on the eleventh and twelfth postpartum days, but she suddenly died on the thirteenth day. Autopsy showed a typical lower nephron nephrosis with pigmented casts.

CASE 4.—*Tubal Pregnancy*: E. L., 46 years of age, gravida iv, was admitted to the hospital. There were no signs of shock or anemia. The next day she was operated upon. The findings were a lacerated cervix, fibroids of the uterus, cystic ovaries, right hydrosalpinx, left tubal pregnancy, and hemorrhoids. The operation consisted of a curettage, a trachelorrhaphy, hemorrhoidectomy, multiple myomectomies, and a bilateral salpingectomy. Following the operation the patient developed urinary suppression with oliguria and died on the third postoperative day. There was no autopsy.

CASE 5.—*Tubal Pregnancy*: M. M., aged 31 years, gravida viii, was admitted to the hospital and operated upon promptly for tubal abortion. The pelvis was found to be full of blood. The operation consisted of a left salpingo-oophorectomy; the patient was given a transfusion of 600 c.c. and parenteral fluids. Following the operation she developed urinary suppression and paralysis of the left arm and leg. Both these conditions persisted until death. The final note on the chart was, "Patient was thrown into acute renal shut-down by the trauma of the tubal abortion." Autopsy showed tubular degeneration of recent origin. The brain showed an infarct of the right frontoparietal region.

CASE 6.—*Rupture of Uterus*: (Reported in previous paper.) R. B., aged 25 years, gravida iv, with breech presentation and slow, difficult labor, was given sedation after 29 hours of poor pains. Eleven hours later, although the cervix was only partly dilated, she was given Pitocin 0.15 c.c. which produced rupture of the uterus. A consultant delivered the baby and placenta, recognized the ruptured uterus and promptly performed a hysterectomy. A tear extended up the right side of the uterus to the fundus with about 300 c.c. of blood in the

## PULMONARY MUCORMYCOSIS COMPLICATING PREGNANCY

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THE obstetrician sets out to deliver a woman successfully of a normal living infant. To accomplish this, he must be on the alert for all possible abnormal signs and symptoms that occur during gestation.

Nausea and vomiting occurring in the third trimester, outside of possible impending eclampsia, usually are associated with other serious conditions, such as appendicitis, intestinal obstruction, peptic and duodenal ulcers, and hyperthyroidism.<sup>1</sup> Other rare conditions are also complicated by nausea and vomiting. As an example, we are presenting a case history of what we believe to be the first case of mucormycosis infection complicating pregnancy, in which the initial complaints were intractable nausea and vomiting.

This 26-year-old Negro para i (Hospital Admission No. 125942), due by dates on June 27, 1947, was first seen for this pregnancy on Nov. 4, 1946, when she was six and one-half weeks pregnant, her last menstrual period having been Sept. 20, 1946. Her initial examination was essentially normal. However, a brown reduction for sugar was noted on her admission urinalysis. Her past surgical history was negative. Her past medical history revealed pneumonia as a child. A positive Wassermann test had been discovered in another clinic in June, 1946, and the patient subsequently had been given penicillin in three daily doses of unknown amount for nine days. Following this, two serological examinations for syphilis were reported negative. The patient ran a normal prenatal course up to 28 weeks' gestation, with a gradual increase in weight from 119 pounds to 130½ pounds. She had a normal blood pressure on her last clinic visit on March 24, 1947. All urine examinations were negative with the exception of a second brown reduction for sugar found at 24 weeks' gestation.

On March 31, 1947, at 29 weeks' gestation, she was admitted to the Boston Lying-in Hospital with a history of upper respiratory infection and cough of one week's duration. Four days before admission, severe epigastric, cramplike pains "coming in waves" developed and were unrelieved by antacids prescribed by her local physician. On the day before admission, the pains increased and intractable vomiting ensued.

Physical examination revealed a thin, lethargic, markedly dehydrated, Negro woman in some abdominal distress. She had lost 13½ pounds since her last clinic visit on March 24th, which was a week before admission. She was difficult to arouse but would respond to painful stimuli. The ears, eyes, nose, and throat were negative. The chest was clear to x-ray. There was slight tenderness and spasm in the epigastrium. The uterus was enlarged to approximately 26 weeks' size and nontender. No other abdominal masses were palpable. Rectally, the cervix was not well made out, although a breech was thought to be presenting. Temperature, pulse, and respiration were normal. Urinalysis revealed one plus albumin, 2 plus diacetic and acetone, with granular casts. Blood pressure was 134/70. Initial blood count revealed a hemoglobin of 70 per cent, white blood count of 9,700 and red blood count of 4.1 million. Sedimentation rate was 2 mm./hr. Icteric index—2.

The patient was treated for her dehydration during the first forty-eight hours but showed no improvement. It became obvious, therefore, that her problem was more than that

tioned earlier, shock causes vasoconstrictive renal ischemia. This ischemia leads to oliguria, which, associated with aciduria, predisposes to precipitation of pigment casts. In the presence of such renal ischemia, myoglobinuria and hemoglobinuria, which cause little injury under normal conditions, result in severe renal injuries (Corcoran and Page).

Once the urinary suppression is established, treatment is directed toward control of the pathologic physiology. However, the renewed interest in this neglected syndrome has been so recent that the therapy offered has not been fully proved or, in the case of nerve block, even tried. There are three therapeutic procedures that seem to offer good prospects of success, namely: urinary alkalization, peritoneal dialysis, and nerve block (splanchnic, high spinal, or caudal anesthesia).

Urinary alkalization, including the use of a diuretic, has been widely studied and definitely decreases the degree of renal injury. Sixth molar sodium lactate is the best preparation, in a dosage of one or more liters daily for alkalization and the best diuretics found so far have been sucrose or mannitol in repeated doses of 5 to 10 Gm. (0.1 Gm. per kg. of body weight), or sodium sulfate (1 Gm. intravenously). Alkaline therapy, so far, has proved of only slight aid and, in fact, it may be possible for an injured kidney to form alkaline urine, so that if the treatment is pushed too far alkalosis may result.

Peritoneal dialysis as a method of removing nitrogenous compounds during the period of renal damage may keep the patient alive until sufficient renal regeneration has occurred. This procedure is based on the fact that the peritoneum is an excellent osmotic membrane, rich in blood supply with a large surface. Flushing it with properly prepared fluids will remove considerable quantities of nitrogenous products. One of us has used this technique successfully in a case of severe transfusion reaction. However, more experience is needed before its usefulness can be evaluated properly.

Splanchnic block, high caudal, or spinal anesthesia has been suggested by Franklin et al.<sup>10</sup> as a method of combating the stimulation of the renal vasomotor nerves which in turn causes the renal ischemia. The authors have had no experience with this procedure but it seems logical and well worth a trial.

### Summary

In a review of the maternal deaths in Philadelphia since the formation of the Maternal Mortality Committee of the County Medical Society seven maternal deaths were found which showed the "crush syndrome" with lower nephron nephrosis. An additional case of twisted ovarian cyst is included in the report. The obstetrical cases included placenta abruptio, ectopic, and birth trauma. Particular stress is placed on prevention of shock or its treatment by early and frequent blood transfusions.

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The right pleural cavity contained 800 c.c. of brownish, cloudy, purulent, slightly foul-smelling fluid. The pleural surfaces were red and injected, with numerous soft, stringy, friable, fibrinous adhesions from the right upper lobe to the parietal pleural surface, especially posteriorly. There were no adhesions or fluid in the left pleural cavity.

The pericardial cavity contained about 50 c.c. of clear, golden-yellow fluid and showed negative serosal surfaces.

The lungs weighed as follows: right lung, 520 Gm.; left lung, 340 Gm. The right lung was of normal size and shape. The pleural surfaces were somewhat dull, pinkish red to purple in color, with filmy fibrinous adhesions on the upper lobe, most marked posteriorly. The upper lobe was rubbery in consistency. On the pleural surface, there were scattered fine cystic blebs measuring approximately 0.1 cm. in diameter, none of which was ruptured. The cut surfaces of the right upper lobe showed a red, homogeneous, wet surface which oozed large amounts of fluid on pressure. The medial aspect of the right upper lobe just above the interlobar fissure revealed a black, homogeneous localized area of softening occupying about one-third of the lobe, which was in contrast to the firm surrounding red area. The right lower and middle lobes were of a dark red color and had a wet red surface which oozed large amounts of fluid on pressure. The whole lung was subcrepitant to firm in consistency, the upper lobe giving an impression of early consolidation, the middle and lower lobes giving an impression more consistent with atelectasis, congestion, and edema. The pulmonary vessels were dissected to their third and fourth branches. A questionable firm reddish-yellow thrombus was noted at the second bifurcation of the right lower lobe vessel. After formalin fixation, a moderate-sized gray, friable, adherent thrombus was found in the artery leading to the softened area in the right upper lobe.

The pleural surfaces of the left lung were pinkish red in color, the consistency being subcrepitant throughout. The cut surfaces showed a reddish purple surface which oozed a moderate amount of frothy, bloody fluid. The pulmonary vessels were not remarkable and contained no thrombi.

The bronchial mucosa was a deep reddish pink color and markedly edematous. The lumen contained a moderate to marked amount of tenacious, reddish-gray, mucopurulent material. The hilar lymph nodes showed moderate anthracotic pigmentation.

The remainder of the gross findings were not remarkable. Dissection of the neck revealed no evident abnormality.

The brain weighed 1125 Gm. The arachnoid was clear, moist, and glistening. There was no adherence to the cortex and no evidence of meningitis or tuberculosis. The brain was symmetrical and of normal consistency. The convolutions were of the normal pattern and the sulci were of normal depth. The vessels were not remarkable.

*Microscopic.*—Eighteen sections of lung were examined. The majority of them showed the usual architecture. The alveoli were generally well expanded. There was only moderate focal atelectasis, moderate amount of cellular debris and edema fluid in the alveoli. There were some small, fibrin thrombi in the arteries which, in general, were moderately congested. The alveolar capillaries also were engorged. In a number of focal areas, collections of polymorphonuclear leucocytes and strands of fibrin in the alveoli were suggestive of early bronchopneumonia. There were also some edema and acute inflammatory cellular infiltration of the pleura in these areas as well. Numerous sections were taken from the soft black homogeneous area of the right upper lobe, and showed an unusual mycotic organism on examination. In the lung tissue showing marked invasion by the mycelia, there was preservation of the alveolar pattern but the cellular detail was very blurred. The alveoli, for the most part, were outlined by eosinophilic granular material without cellular detail and by hemosiderin which outlined the position of the alveolar capillaries. There was abundance of cellular debris and edema fluid in the alveolar spaces. The pleura was markedly thickened and edematous. There was a fibropurulent exudate on the surface containing many polymorphonuclear neutrophils. Numerous large, tubular structures with thin basophilic staining walls could be seen, in which very rare septae were present. There was marked branching of the hyphae which seemed to contain a coarse, granular, basophilic material. (See Figure 1, A, B, C.) Occa-

of severe vomiting at the 26th week of pregnancy. Her urine albumin gradually rose from one plus to three plus on the day of her death. The various blood and urine studies during the course of hospitalization are presented in Table I.

TABLE I. LABORATORY DATA

Urine								
DATE	ALBUMIN	SUGAR			DIACETIC	ACETONE		
March 31	1 plus	0			2 plus	2 plus		
April 2	2 plus	Br. Red				1 plus		
April 3	1 plus	Br. Red				1 plus		
April 4	1 plus							
April 5	2 plus	Br. Red				0		
April 6	3 plus	Green with sediment				0		
Blood								
DATE	CO <sub>2</sub> COMB. POWER	T. P.	NPN	BL. SUGAR	CHLORIDES	HGB. PER CENT	RBC	WBC
March 31						70	4.10 M	9,700
April 2	38 vol. %		56	247 mg. %		118	5.05	10,900
April 3	20 vol. %	4.9	68	282 mg. %	114m/Eq/L	110	5.01	9,600
April 4	36 vol. %	4.2	67	270				
April 5	36 vol. %		104	300		117	4.96	6,800
April 6		4.2	88	252		99	3.400	9,300

On the third hospital day the patient became more drowsy, despite intravenous fluids. Her blood pressure rose to 170/80. The neurological signs were negative. A lumbar puncture was performed, revealing an initial pressure of 190 mm. of water with normal dynamics and pulse wave. The fluid was clear, protein 8.4 mg. per cent. There were no cells and the Hinton test was negative. On the fourth hospital day, because of increasing stupor, the neurological consultant stated: "The patient is stuporous without lateralizing neurological signs. The most likely explanation of this condition is the acidosis and uremia. There are no signs at present of focal brain disease, though these could be masked by the stupor." Because of the stupor and lack of lateralizing neurological signs of a brain lesion, the consultant made a diagnosis of diabetes mellitus, and renal disease of undetermined type. (Two cephalin-flocculation tests for liver damage were negative.) Laboratory data are summarized in Table I.

On the fifth hospital day the patient apparently started up in labor, and simultaneously developed a temperature of 100.8° F. (R) for the first time. A sterile pelvic examination was performed and the cervix was found to be two fingers dilated; accordingly, a foot was brought through the cervix and a fillet attached. This was done in the hope of shortening labor and perhaps easing the load on the kidneys. One hour and twenty minutes later the patient delivered herself of a 2 pound, 4½ ounce macerated stillborn male infant. The placenta was delivered uneventfully.

Following delivery, the temperature rose to 103.2° F. (R). Respirations continued to rise to 45 per minute. The patient failed to improve and died on April 7, 32 hours post partum, seven days after admission to the hospital, and thirteen days after the onset of symptoms.

An abstract of the pathologic report follows:

Gross.—The body was that of a well-developed, fairly well-nourished, Negro woman measuring 66 inches in length.

The peritoneal cavity contained about 50 c.c. of clear, golden-yellow fluid, although the serosal surfaces were not remarkable. Inspection of the organs in situ revealed essentially normal findings, except for a spleen which was slightly smaller than normal and a ptotic loop of transverse colon. There was a bright reddish-purple, boggy, postpartum uterus extending 12 cm. above the symphysis. The pelvic organs were otherwise not remarkable.

Sections of liver, spleen, kidney, bladder, breast, and thyroid were not remarkable.

All the pathological sections, including the brain and placenta, were carefully examined for the presence of mycelial hyphae and none were found except in the sections of the lung.

Cultures of right pleural fluid, lungs, pericardial fluid, and heart blood, were planted on routine blood agar plates, thioglycollate and broth. All these cultures showed only growth of *Bacillus coli* and *Staphylococcus aureus*. Fungus infection was not suspected and therefore no suitable cultures for its detection were planted.

Dr. C. W. Emmons,<sup>2</sup> Principal Mycologist, U. S. Public Health Service, kindly reviewed sections of the lung and has allowed us to quote his letter as follows:

"Since cultures were not made, the fungus cannot be positively identified. I agree with your opinion that it is probably *Mucor*. The size of the hyphae, profusion and type of branching, infrequent septation, and multinucleate cells are consistent with that fungus, and in these respects there is a resemblance to similar structures in material from other cases I have seen which were provisionally diagnosed as mucormycosis."

### Discussion

Mucormycosis is, indeed, a rare disease in man. These fungi are of the Class of Phycomycetes, order Mucorales, in the family of Mucoraceae, which is parasitic in animals and man. Gregory, Golden, and Haymaker,<sup>2</sup> in 1943, reviewed the subject and reported three cases of mucormycosis involving the central nervous system, the original cases being characterized by a triad of infection of the orbit, uncontrollable diabetes and the presence of mucor mycelia in thrombosed cerebral vessels. LeCompte and Meissner<sup>4</sup> added a fourth case involving the central nervous system and demonstrated the typical triad. There have been ten cases reported in the literature involving the lung only,<sup>3</sup> this location being the most common; the central nervous system the least common.

This case is of interest because of the initial complaints of intractable nausea, vomiting, and pain in the third trimester of pregnancy. During her prenatal course she had on two occasions a brown reduction for sugar which was never thoroughly investigated. The question naturally arises: Did this patient have mild, uncontrollable diabetes and subsequently became infected by a fungus which found a fertile field for growth? This question is unanswerable, although one cannot help but wonder if, had more attention been directed to this isolated urinary finding early in pregnancy, this maternal death might have been prevented. It is presented to stimulate consideration of obscure infection, such as mycosis, in unexplained nausea and vomiting in the third trimester of pregnancy.

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sional multinucleated cells were noted. The mycelial structures were very numerous and were present both in the pleura and underlying lung tissue. One section showed a definite, recent, pulmonary infarct with the characteristic microscopic findings. Section of the pulmonary artery supplying the area of the infarct showed a large, antemortem thrombus with massive invasion of the the thrombus and of the vessel walls by mycelial hyphae. Numerous other sections of lung show findings consistent with marked pulmonary edema and moderate pulmonary emphysema.

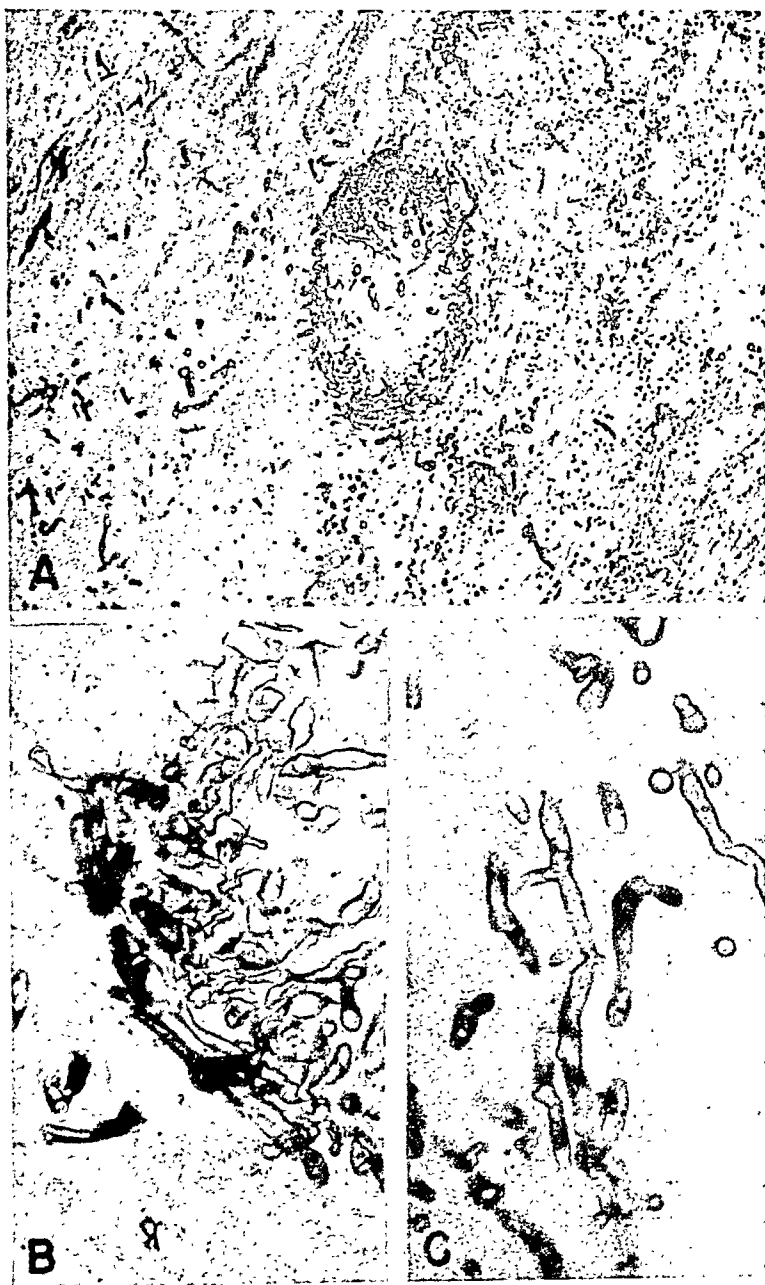


Fig. 1.—A. Shows massive invasion of lung and thrombosis of vein by mycelia. (100 $\times$ ).

B. Shows high power view of vein in Fig. 1A, demonstrating infrequent septation and branching of the mycelial structures. (400 $\times$ ).

C. Shows numerous branching of hyphae with infrequent septation in necrotic lung tissue. (400 $\times$ ).

Two sections of pancreas showed the usual irregular lobular arrangement of small compact acini. There was no evidence of the pathological findings which are usually felt to be consistent with diabetes.



Larson and his co-workers,<sup>5, 6, 7</sup> as well as Reasoner<sup>8</sup> and Spencer,<sup>9</sup> have done some investigative work on the sodium salt of ricinoleic acid. Larson et al., in their studies of the effect of surface tension of the menstruum upon bacteria and toxins, have shown that virulent strains of organisms (*Bacillus tuberculosis*, *Diplococcus pneumoniae*, and *Streptococcus viridans*) can be rendered nonvirulent when suspended in solutions of sodium ricinoleate. Larson is of the belief that the soap, by lowering the surface tension of the menstruum, causes the bacteria to be more readily "wetted," and when the bacteria are introduced into the body their union with the specific antibodies is enhanced. Larson did not regard the action of soap as involving a true chemical union, nor did he make note of any physical changes in the bacteria themselves.

Reasoner<sup>8</sup> has suggested that soap lather may be responsible for the rarity of the occurrence of extragenital lesions. He observed that when a suspension of *Treponema pallidum* was mixed with certain commercial soap solutions motility was inhibited at once, and the organisms became swollen, distorted, and reduced in number.

Spencer's<sup>9</sup> observations have shown that the density of suspensions of certain species of bacteria is reduced to zero by appropriate solutions of sodium ricinoleate, while the density of other suspensions is greatly increased. Apparently the reaction is an effect not dependent upon the surface tension nor upon the hydrogen ion concentration of the menstruum.

### Clinical Study

In this report the results obtained in a study of 98 patients suffering from vaginal mycosis are presented. Before the institution of therapy an unlubricated speculum examination was made, and a moist-drop preparation was taken for microscopic confirmation of the diagnosis. In the questionable cases the vaginal contents were cultured on Sabouraud's agar medium, and the plates were read in 24 to 48 hours.

All patients were treated by a single method—namely, the vaginal instillation of the 3 per cent ricinoleic acid preparation. Approximately 5 c.c. of jelly were deposited deep into the vagina daily (on retiring) by means of a plastic syringe similar to those used in the instillation of contraceptive jelly. No douches or other medications of any kind were used during the course of this treatment. Abstinence from coitus was advised during the period of treatment.

All patients presenting symptoms or abnormal findings in the vaginal secretions were referred to a special clinic. The single constant complaint of patients with vaginal mycosis was pruritus. Other symptoms were burning about the introitus and rectum, dyspareunia, mild leucorrhea free of odor, and caseous-like material about the introitus and vagina. The pruritus varied from a mild to a severe unrelenting itch. The burning generally coincided with the degree of pruritus. Dyspareunia was present in the majority of the severe cases. The leucorrhea was predominantly scanty. The vaginal material is thick, white, or occasionally yellowish, caseous-like or "thrush" patches on the vaginal walls. The presence of this material is accompanied by a moderate to severe inflammation and edema of the vulva. Cervical erosions, cervicitis, polyps, and other common causes of leucorrhea were frequently found as incidental lesions.

### Investigational Data

Table I shows the total number of patients treated with 3 per cent ricinoleic acid jelly. Of this number 68 were gravid, while 30 were nonpregnant women. On further investigation of the nonpregnant group it was found that 5, or 17 per cent, of these patients gave a history as well as clinical evidence of having

## THE SPECIFIC TREATMENT OF VAGINAL MYCOSIS

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VAGINAL mycosis continues to be an annoying problem even with all the innumerable agents which are available to the physician today. The causative organisms belong to the medical monilia group known commonly as *Monilia albicans* or *Candida albicans*.<sup>1</sup> These fungi are frequently found in the mouth, vagina, and intestinal tract of the normal individual.

Vaginal mycosis occurs predominantly during pregnancy. It is assumed that the increased amount of glycogen-like material present during gestation favors the growth of the *Candida albicans*. Exceptions to this will be found in patients in whom the common sugars (lactose excluded) are used for vaginal trichomoniasis therapy, or in postmenopausal individuals on excessive estrogenic therapy. Diabetes is another predisposing factor because the infection is related directly to the glycosuria, and thus it will be encountered ordinarily in the uncontrolled diabetic patient. The symptoms in the gravid patient disappear immediately after delivery. Fungi may be isolated from the vagina in 14 to 41 per cent of patients depending upon the type studied.<sup>3</sup> It is conservative to estimate that 25 per cent of all pregnant patients harbor these fungi in the vagina. A fair percentage of the group will develop mycosis. The sporadic case of oral thrush is most likely the result of oral contamination during delivery. From these facts it is evident that these organisms are opportunists.

One of the patients in our Out-Patient Clinic reported the symptomatic improvement of her vaginal mycosis following use of a contraceptive jelly. This led Hesselstine<sup>2</sup> to a thorough investigation of all the ingredients of this jelly against a medical monilia (No. 6225). The technique of Hesselstine and Hopkins<sup>4</sup> was employed. Through this work it was found that ricinoleic acid held promise as a fungicide for the medical monilia. The buffered acid (pH 4.5) jelly was found to be nonfungicidal.

### Ricinoleic Acid and Salts

A study was instituted to evaluate the practical application of ricinoleic acid in the treatment of vaginal mycosis. A tragacanth-acacia buffered jelly was used as the vehicle for the ricinoleic acid. The concentrations investigated were 0.75 per cent, 1.5 per cent, 2 per cent, and 3 per cent. All concentrations in vitro revealed fungicidal behavior.

On pilot studies, 3 per cent ricinoleic acid was tolerated satisfactorily. It gave relief more quickly than the weaker concentrations and the commercial contraceptive jelly which contained 0.75 per cent ricinoleic acid. It is believed that the ricinoleic acid could be equally effective if used in some other type of vehicle, such as a vaginal suppository.

thrush in the newborn as a consequence of contamination during parturition.<sup>10</sup> Another important quality is the simplicity of its application. This reduces the number of office visits and furnishes adequate treatment, directed by the physician, through daily self-administration.

TABLE II. DURATION OF TREATMENT UNTIL ASYMPTOMATIC

TIME	PREGNANT		NONPREGNANT	
	NO.	PER CENT	NO.	PER CENT
72 hours	18	36	7	26
1 week	18	36	17	63
2 weeks	9	18	1	4
3 weeks	4	8	2	7
4+ weeks	1	2	0	0

TABLE III. TOTAL LENGTH OF TREATMENT

DURATION	PREGNANT		NONPREGNANT	
	NO.	PER CENT	NO.	PER CENT
1 week	0	0	0	0
2 weeks	6	9	3	10
3 weeks	5	7	5	17
4 weeks	11	16	2	7
5 weeks	10	15	1	3
6 weeks	6	9	8	27
7 weeks	6	9	1	3
8 weeks	6	9	2	7
9-12 weeks	10	15	7	23
13-16 weeks	6	8	0	0
17+ weeks	2	3	1	3
	68		30	

TABLE IV. WEEKS OF GESTATION WHEN TREATMENT WAS INITIATED

TIME OF GESTATION	NUMBER OF CASES	PERCENTAGE
0-4 weeks	1	1
5-9 weeks	0	0
10-14 weeks	6	9
15-19 weeks	15	22
20-24 weeks	13	19
25-29 weeks	16	24
30-34 weeks	14	21
35-39 weeks	3	4
40 weeks	0	0
	68	

TABLE V. AGE INCIDENCE

AGE	PREGNANT		NONPREGNANT	
	NO.	PER CENT	NO.	PER CENT
15-19 years	4	6	0	0
20-24 years	26	38	2	7
25-29 years	18	26	4	13
30-34 years	16	24	13	43
35-39 years	4	6	8	27
40-44 years	0	0	2	7
45-49 years	0	0	1	3
	68		30	

had vaginal mycosis in a recent pregnancy. As shown in Table I, 74 per cent of the pregnant group and 90 per cent of the nonpregnant group were considered cured. The failures occurred in 26 per cent of the pregnant group and in 10 per cent of the nonpregnant group.

An analysis of the nonpregnant failures discloses that all three patients used the 3 per cent ricinoleic acid jelly only sporadically. They would use it until relieved of their acute distress, then cease treatment. Consequently this group was intermittently troubled with vaginal symptoms. Even so, all of this group remained free of their symptoms when employing the material under study. Failures in the pregnant group totaled eighteen, with fourteen using the medication only sporadically. Hence only four were definite failures. The majority of this group were symptom free within 48 to 72 hours after the institution of the therapy. Symptoms recurred in one to four weeks if the patient was not cured at the time of interruption of therapy. All patients remained symptom free while on the medication. From the gravid group, four women used the medication irregularly until delivery.

TABLE I. VAGINAL MYCOSIS

TOTAL NUMBER STUDIED 98		CURED	FAILURES
Pregnant	68	50 (74%)	18 (26%)
Nonpregnant	30	27 (90%)	3 (10%)

It is shown in Table II that 36 per cent of the pregnant group and 26 per cent of the nonpregnant group became asymptomatic within 72 hours. Within one week 72 per cent of the pregnant group and 89 per cent of the nonpregnant group were asymptomatic.

The majority of cases were cured in two to eight weeks. Only a small percentage of the cases required nine or more weeks of therapy. Most cases will respond well within two to four weeks of therapy. A few cases were treated for longer periods during the early phases of this study to determine if there might be any tissue intolerance or untoward effect upon the pregnancy. Another small group of patients required longer periods of treatment because they used the 3 per cent ricinoleic acid jelly incorrectly.

In pregnancy the majority of the mycotic infections developed in the second trimester (Table IV).

The incidence of the infection in relation to the patient's age does not seem particularly significant especially as the age frequency for all pregnant patients in the Clinic has not been determined during this study but these data are presented in part of the protocol (Table V).

Comments

Ricinoleic acid 3 per cent in a buffered acid jelly vehicle is believed to be the medication of choice in the treatment of vaginal mycosis. It produces results superior to any method which has been tried in this clinic. (Propionate compound jelly has not been tried as our study was underway prior to its report.<sup>11</sup>) Ricinoleic acid in 3 per cent concentration in tragacanth-acacia jelly is a stainless, odorless, nonirritating, and efficient compound which is easily applied by means of a plastic syringe. The jelly's consistency at body temperature, adhesiveness, and wetting power permit it to come in intimate contact with the entire vaginal mucosa. In most instances it gives the patient complete relief from the intense pruritus within 72 hours and causes a disappearance of the causative organism in due time. This action should reduce the risk of oral

combinations in a base jelly. A report of these studies will be made. The combination of 3 per cent ricinoleic acid and 0.1 per cent oxyquinoline sulfate gave excellent results as indicated in the body of the paper.

The authors thank the Ortho Research Foundation for their cooperation for the generous supplies of materials which were prepared at our suggestions.

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The ricinoleic acid jelly has been used over prolonged periods without any ill effects. There has been no evidence of any sensitivity or intolerance to this preparation in this vehicle. Likewise, there have been no untoward accidents in the mothers or the newborn following its use. This therapy has been used until near term in a number of instances.

The criterion for cure is the absence of the clinical and symptomatic signs of vaginal mycosis together with the failure of recurrence of the infection after discontinuance of treatment. Cultures have been used in many, but the mere presence of a particular organism is not proof of an active infection.

The causative organism, *Monilia albicans*, is frequently found in the mouth, vagina, intestinal tract, and on the skin. These sites may easily serve as foci for reinfection, with the gastrointestinal tract being the principal offender. Active colonization of some portion of the intestinal tract has been demonstrated by Benham and Hopkins,<sup>12</sup> who have obtained positive cultures from this source for periods of over a year. The frequent scratching of the perirectal and perivulvar-cutaneous surfaces, faulty anal hygiene, and the contact of tight garments constitute excellent methods of reinoculation of the vulva.

Monilial infections involving other cutaneous areas in association with vaginal infections have been noted.<sup>13</sup> These are usually on the breasts of women, and more rarely on the penis of the conjugal partner. Such infections could and probably usually do result from the transference of fungus material from the vulva and vagina. In view of the fact that the incubation period of oral mycosis varies from 24 to 96 hours, and the vaginal incubation time should be comparable, some of our failures must be considered as reinfections.

One cannot stress too strongly the tremendous importance of strict personal hygiene; consequently prophylaxis is important.

### Summary

1. A new and specific therapy for vaginal mycosis is described, namely, the use of ricinoleic acid 3 per cent in a buffered acid jelly.

2. This course of therapy in an uncorrected series produced 74 per cent of cures in the pregnant group and 90 per cent of cures in the nonpregnant group.

3. This method of therapy is characterized by prompt relief of the pruritus, disappearance of the causative organism, and prevention of spread of infection to other skin surfaces.

4. No ill effects or accidents have occurred over extended periods of treatment to either the mother or newborn.

5. Use of this preparation affords a convenient and most satisfactory method of self-treatment for the patient.

6. It is believed that the 3 per cent ricinoleic acid could be carried in suppositories or other suitable vehicles.

7. The skin, mouth, and intestinal tract serve as ready foci for reinfection of the vagina.

### Correction

The summarization above *may or may not be* valid in assigning credit exclusively to ricinoleic acid as the specific fungicidal agent. The manufacturing pharmacist added oxyquinoline (0.1 per cent) as a preservative without approval and without informing either the authors or the medical director of Ortho Research Foundation. The fact that oxyquinoline was added came to light shortly before the galley proofs arrived.

Since oxyquinoline sulfate does possess some fungicidal action, an investigation was begun immediately to evaluate ricinoleic acid and oxyquinoline sulfate separately and in

In addition, certain specific tests are necessary for the diagnosis of functional sterility. These tests consist of the following:

1. Endometrial biopsies
2. Vaginal smears
3. Basal temperature graphs
4. Estimation of the urinary gonadotropins

Endometrial biopsies usually reveal an abnormal pattern. Atrophic, proliferative, or hyperplastic endometrium is found when a secretory phase should be present premenstrually. In some patients, a secretory phase is found throughout the cycle and this, also, is abnormal, indicating a retained corpus luteum.

Vaginal smears and basal temperature graphs usually but not always parallel these abnormal endometrial findings.

The estimation of urinary gonadotropin is valuable inasmuch as an elevated gonadotropic titer indicates primary ovarian deficiency with compensatory pituitary overactivity. Absence of minimal amounts of urinary gonadotropin point toward pituitary insufficiency.

### Methods of Treatment

After a thorough physical examination and completion of the laboratory investigations, as mentioned above, treatment is instituted and carried out according to a definite plan. Thyroid medication is given when indicated. Dietary adjustments are made, emphasizing the advisability of a high protein, low fat and carbohydrate diet in obese patients. In slim, hypotonic patients, a high caloric diet supplemented by vitamins and small daily doses of insulin is advised. If no results are obtained within a reasonable period of time, hormonal therapy is instituted. If there is still a lack of response within six to eight months, "small dose" radiation therapy is administered.

Many of the patients refuse radiation therapy and hormonal therapy is carried out for longer periods with intervals of rest. Another group of patients who never received hormonal therapy preferred the shorter, less expensive, and less tedious course of radiation therapy.

The criteria of success of either endocrine or radiation therapy consist of achieving pregnancy in sterility cases and of re-establishment of normal menstrual cycles in the unmarried women with secondary amenorrhea.

### Endocrine Therapy

The endocrine therapy consisted chiefly of anterior pituitary or equine gonadotropins\* supplemented by chorionic gonadotropins administered simultaneously or sequentially. Only adequate intensive therapy could be expected to be of any value; casual and irregular treatment is useless and succeeds only in discrediting the value of hormonal therapy. The equine gonadotropins are administered in doses of 200 to 500 international units for from 4 to 6 injections daily or every other day, in the first half of the cycle. Anterior pituitary gonadotropins are administered in a similar manner. Chorionic gonadotropins are administered in the second half of the cycle or combined with the anterior pituitary in the first half of the cycle.

\*The equine gonadotropin was supplied by courtesy of Dr. W. H. Stoner of the Schering Corporation in the form of Anteron and of Dr. Murray Scott of Ayerst, McKenna and Harrison as Antex. Antex Leo was supplied by courtesy of Dr. Claire Folsome of the Ortho Research Foundation. Anterior pituitary gonadotropin, A. P. L., was supplied by courtesy of Dr. Murray Scott of Ayerst, McKenna and Harrison.

# EVALUATION OF HORMONAL AND RADIATION THERAPY IN 190 CASES OF FUNCTIONAL STERILITY AND SECONDARY AMENORRHEA

## Preliminary Report

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IT HAS been estimated that involuntary sterility occurs in about 17 per cent of all marriages.<sup>1</sup> Most clinicians agree that the male is at fault in about 40 per cent, the female in about 50 per cent, and both partners in about 10 per cent of infertile marriages.

In the female there are many conditions which contribute to sterility, especially, tubal and ovarian pathology, genital abnormalities, general systemic diseases, and nutritional deficiencies. The influence of nervous shock, anxiety, and mental diseases on infertility is also well known. During the first and second World Wars the effect of shock, strain, and anxiety on the physiology of the female pelvic organs has been thoroughly studied and its injurious effects demonstrated.<sup>2</sup>

Among other causes which frequently play an important rôle in sterility are: thyroid dysfunctions, pancreatic disturbances, particularly diabetes, and metabolic and endocrine disturbances.

This presentation, however, deals with endocrine disturbances of the pituitary-ovarian hypofunction type with clinical manifestations of sterility, secondary amenorrhea, and dysfunctional uterine bleeding, without any evidence of organic pathology. Such type of sterility is designated as "functional" or endocrine sterility.

Since secondary amenorrhea is associated with functional sterility in 94 to 96 per cent of cases,<sup>3</sup> and since these conditions for the most part have a common etiological basis, it is wise to consider them simultaneously.

It is the purpose of this paper to evaluate the relative merits of endocrine and radiation therapy in a series of 130 cases with functional sterility and 60 cases with secondary amenorrhea in women of a younger age group.

## Diagnosis

The question arises as to how one arrives at a diagnosis of functional sterility. This diagnosis is made only after the status of the husband has been established and a thorough physical examination of the wife has ruled out systemic diseases, organic pelvic pathology, and mental and nervous diseases. The presence of tubal patency must be established by means of a Rubin test, salpingogram, or both. Basal metabolism, estimation of the specific dynamic action of the proteins, a Wassermann test, and a complete blood count are routine procedures in every case.



The greatest majority of our patients were treated by the modification of this technique as follows\*:

Two hundred kilovolts therapy was employed with 0.6 mm. copper and 1 mm. aluminum filtration at 50 cm. target-skin distance. The half value layer was 1 mm. copper. The ovarian fields were 8 by 10 cm. and the pituitary fields 6 by 8 cm. A vaginal examination was performed in all married women and the exact location of each ovary was marked on the skin of the anterior and posterior pelvis. In unmarried women, the ovarian location was approximated by means of rectal examination. In most of the cases four treatments were given within a total interval of two weeks. The first treatment was delivered to the anterior right and left ovary, the second to the right lateral pituitary field, the third to the posterior right and left ovary and the fourth to the left lateral pituitary area. The skin doses were so calculated as to deliver a total of 80 r. into each ovary and into the pituitary gland. A few of the patients received similar therapy in weekly treatments over a period of three weeks. As far as possible the technique was kept constant for purposes of investigation.

It is understood that proper precautions must be taken before instituting radiation therapy. In secondary amenorrhea it is imperative to do a Friedman test before starting. In menstruating women therapy should be started immediately after the menses. Marital relations should be forbidden during the course of therapy. These precautions preclude the possibility of irradiating a women who may already have conceived. Results of radiation therapy are analyzed in Tables I, II, and III.

TABLE III. TIME INTERVAL BETWEEN RADIATION AND DIAGNOSIS OF PREGNANCY

Within 2 months	9 cases
Within 3 months	1 case
Within 4 months	2 cases
Within 6 months	2 cases
Within 7 months	3 cases
Within 10 months	2 cases
Within 1 year	1 case

### Discussion

In our series of 76 patients treated with endocrine therapy, conception occurred in 26 patients or 34.2 per cent (Table I). Some clinicians report higher percentages of success. Winston,<sup>21</sup> reported conception in 44 per cent of cases, Hall,<sup>6</sup> in 55 per cent. Davis and Koff,<sup>22</sup> Siegler,<sup>23</sup> and Campbell and Sevringhaus<sup>24</sup> report favorable results with pituitary and equine gonadotropins. Rydberg<sup>7</sup> stated that the administration of equine and chorionic gonadotropins in suitable dosages almost always corrects secondary amenorrhea and functional sterility. Other workers, however, report poor results with equine and chorionic gonadotropins.<sup>25, 26</sup> Our results with endocrine therapy fall midway between the enthusiasm of the former workers and the pessimism of the latter. In view of a rather fair percentage of success which may be obtained with endocrine therapy I feel that patients should be given an adequate trial with hormonal therapy before radiation is attempted. Although there have been no untoward results on the offspring of the first generation of those treated with radiotherapy, possible genetic mutations in the third or fourth generation must be considered.

There is one point which is worthy of note in passing: Four patients who did not conceive re-established a normal endometrial pattern. Although this

\*Great appreciation is extended to Drs. Milton Friedman and Carye-Belle Henle who treated the majority of our patients with radiation therapy. We also express our appreciation to Dr. Louis Levenson who treated some of the patients in this group.

The variations in these techniques have been evolved by Hamblen,<sup>4</sup> Mazer,<sup>5</sup> Hall,<sup>6</sup> Rydberg,<sup>7</sup> Hawkinson,<sup>8</sup> and others. While we used several variations suggested, our best results were obtained with the Rydberg technique.

The possibility of forming antihormones must be remembered when large doses of either anterior pituitary or equine gonadotropins are used. According to Leatham and Rakoff,<sup>9</sup> equine gonadotropins develop specific antihormones after prolonged use of large doses. Nonspecific antihormones may be produced by anterior pituitary gonadotropins. In order to avoid this possibility which would negate the value of the therapy, these hormones should be used in large doses for short specified periods. The use of pituitary and equine gonadotropins should be alternated and a period of rest should be allowed after each series.

The above stimulative therapy will not achieve the desired results if the receptor organs (the uterus and the tubes) are hypoplastic. It is, therefore, necessary in such cases to produce growth and development by a pretreatment with sex steroids, such as estrogens and progestin. Results of endocrine therapy are analyzed in Tables I and II.

TABLE I. FUNCTIONAL STERILITY

1. Age	19 to 37 years	Average age, 27 years
2. Duration of Sterility	2 to 13 years	Average, 4½ years
3. Endocrine Therapy	76 cases	Conception 26 cases (34.2%) Miscarriages 4 cases
4. Radiation Therapy	54 cases	Conception 20 cases (35.2%) Miscarriages 2 cases
	37 endocrine resistant 17 radiation only	Conception 12 cases (32.5%) Conception 8 cases (47%)

TABLE II. 60 CASES OF SECONDARY AMENORRHEA IN UNMARRIED WOMEN

1. Age	16 to 29 years	Average age, 21 years
2. Interval between periods	4 months to 3 years	Average, 7 months
3. Endocrine therapy	32 cases	40.6% re-established periods
4. Radiation therapy	28 cases	46.4% re-established periods

*Note:* Of the 28 radiation therapy cases, 23 had previous endocrine therapy and 5 had no previous endocrine therapy.

### Radiation Therapy

Irradiation of the pituitary and ovarian regions for the relief of "functional sterility" in the female is a universally accepted therapeutic procedure.

This therapeutic approach to the problem of sterility originated in Europe, when Halberstaedter,<sup>10</sup> established the selectivity of the x-rays for the ovary in 1905 and Beclere,<sup>11</sup> in 1926, reported the beneficial effects of roentgen irradiation of the pituitary in a case of secondary amenorrhea.

In this country, Rongy<sup>12</sup> and Rubin<sup>13</sup> were the first to apply this form of therapy in cases of functional sterility and secondary amenorrhea. In 1926, Rubin reported his first series of nine cases with a high percentage of successes; he later induced Kaplan, a radio-therapist, to extend this form of therapy to a large group of suitable cases with very encouraging results.

Several other clinicians and radiologists, Edeiken,<sup>15</sup> Mazer,<sup>16</sup> Finkler and Friedman,<sup>17</sup> Friedman and Finkler,<sup>18</sup> Hanman,<sup>19</sup> and Dripps,<sup>20</sup> applied this form of therapy and reported from 40 to 50 per cent successful results.

The original technique used by Kaplan was carried out by several clinicians with only slight variations in the dosage and number of treatments.

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indicates partial response to therapy it cannot be included in this group of successful cases.

Of the group who were treated by means of endocrines, four of the twenty-six conceptions resulted in abortion. This figure of about 15 per cent can be considered within the normal range of expectation.

In reference to secondary amenorrhea (Table II), our figures of re-establishment of menses in 40.6 per cent of cases are in agreement with those of many other workers. It is to be noted that the average age is 21 as compared to 27 years in those with functional sterility. It is, therefore, logical to assume that in the younger age group the end organs are more receptive to endocrine stimulation.

In reference to radiation therapy for functional sterility (Table I), twenty out of a total of fifty-four cases conceived (35.5 per cent). It must be noted that seventeen of the fifty-four cases had previously been treated with endocrine therapy and must be considered as endocrine resistant. Considering that these posed a more difficult problem from a therapeutic point of view, this percentage of success cannot be used as a true index of the value of radiation therapy. A more justifiable evaluation would be from a series of cases which had no previous endocrine therapy. Of 17 patients in this group, eight, or 47 per cent, conceived.

In the irradiated group, of the twenty patients that conceived, there were only two miscarriages (10 per cent), a figure which is well below the normal expectancy.

We were impressed with the rapidity of response to radiation therapy and analyzed the twenty women who conceived (see Table III). As seen from the table, nine patients conceived within two months and of this group four conceived within six weeks. The promptness with which conception followed the therapy demonstrated that the success is not a coincidence.

It is impossible to prepare such a table for endocrine therapy because this type of treatment is more prolonged and more difficult to evaluate.

Again, in secondary amenorrhea, as in functional sterility, radiation therapy has proved to be more successful in our 28 cases, 23 of which were endocrine resistant. In 46.4 per cent, normal menses were re-established.

### Conclusions

1. One hundred thirty cases of functional sterility and sixty cases of secondary amenorrhea are reviewed for the purpose of evaluating the relative merits of hormonal and radiation therapy; one hundred eight cases were treated with endocrine therapy and eighty-two cases with radiation therapy.

2. In functional sterility, conception took place in 34.2 per cent of patients treated with hormones and 35.2 per cent treated with radiation.

3. In secondary amenorrhea, periods were re-established in 40.6 per cent of patients treated with hormonal therapy and 46.4 per cent of patients treated with radiation therapy.

4. Although radiation would appear to be ideal because of the high percentages of success, more rapid response and economy, great care must be exercised in the proper selection and study of cases considered for radiation therapy.

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infant. This is slightly higher than the general incidence of primigravidas and primiparas. There was also a slight increase in the incidence of premature rupture of the membranes among patients of high gravidity and high parity.

*Gestation Period.*—Forty-eight patients were at term, thirty-four in the eighth month, fifteen in the seventh month, and five in the fifth and sixth months of pregnancy.

*Time Interval.*—The length of time between rupture of the membranes and the onset of labor varied from less than one hour to fifty-six days. Rupture of the membranes occurred most frequently (thirty-three cases) between twenty-four hours and forty-eight hours before the onset of labor.

*Cause.*—In all instances, rupture of the membranes was spontaneous. There was no history of trauma or other apparent predisposing cause.

*Toxemia.*—There were only seven pre-eclamptic patients. This is lower than the average incidence.

*Induction of Labor.*—In 65 cases the onset of labor was spontaneous. There was induction with castor oil (in a few instances quinine was added) in thirty-one cases; there was induction by Pituitrin in one case, and there was bag induction in five cases.

*Duration of Labor.*—The average duration of labor showed no increase nor decrease from the average length of labor in cases without premature rupture of the membranes. However, the mode showed a shorter duration of labor. Cases in which the length of labor was increased were those in which abnormal presentations or disproportion was present.

*Presentation.*—In eighty-four cases there was vertex presentation; in sixteen cases, breech presentation, and in four cases, transverse presentation. There were two sets of twins in this series.

Prolapse of the cord occurred in seven cases. Prolapse of an arm occurred in three cases.

*Type of Delivery.*—The methods of delivery were as follows:

Spontaneous vertex	61
Elective low forceps	6
Operative forceps	10
Internal podalic version and extraction	
From vertex presentation	5
From transverse presentation	3
Dührssen's incision and operative forceps	1
Spontaneous breech	3
Breech aided	7
Breech extraction	6
Spontaneous evolution aided	1
Cesarean section	1

Uterine insertion of Braun bag was employed for cervical dilatation in eight cases.

*Maternal Morbidity.*—There were three cases of prepartum fever, twelve cases of intrapartum fever, and eighteen cases of postpartum morbidity. The longest period of hospitalization post partum of any case was eighteen days. One patient had pyelitis post partum. In one instance, a stitch abscess developed in the episiotomy wound.

In correlating fever or morbidity with the length of time between rupture of membranes and onset of labor, it was found that all three cases of prepartum fever occurred in the 24 to 96 hour period. Seven of the twelve patients with intrapartum fever were in the 24 to 72 hour group. Among the eighteen patients who had postpartum morbidity, ten were in the 1 to 12 hour period, five in the 12 to 72 hour period, three in the 72 to 240 hour period, and none in the period over 240 hours.

## PREMATURE RUPTURE OF THE MEMBRANES\*

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**P**REMATURE rupture of the membranes by definition is the rupture of the membranes at any time before the onset of labor.

The incidence of premature rupture is stated by recent authors of large series of cases to be higher than 10 per cent. This seemingly high incidence is due to strict adherence to the definition. In about 60 per cent of the cases of premature rupture of the membranes the onset of labor is almost simultaneous with rupture; in a large portion of the remaining 40 per cent labor starts within several hours after rupture.

### Material and Methods

A survey is presented of 102 patients with premature rupture of the membranes at the Cincinnati General Hospital over the period from January, 1936, to May, 1941. The total number of deliveries in these years was approximately 12,800. In reviewing the histories catalogued as premature rupture of the membranes, many had to be discarded because they were not instances of premature rupture of the membranes, but rather, rupture of the membranes early in labor. Obviously, the greater percentage of premature rupture of the membranes was not catalogued at all. Failure to catalogue premature rupture of the membranes appears to be a common offense. It seems especially easy to neglect to record this fact when the rupture of the membranes was followed shortly afterward by the onset of labor or when the patient had a favorable and uncomplicated course. Therefore, in this small series of cases there is a disproportionately high incidence of prolonged periods between rupture of the membranes and the onset of labor and a disproportionately large number of complications. This does not necessarily imply a correlation between length of time of rupture of the membranes and complications of labor and delivery, because in many patients with complications rupture of the membranes preceded the onset of labor by a short interval.

Data compiled from this series include: age, color, gravidity, parity, gestation period, length of time between rupture of the membranes and onset of labor, trauma or any other apparent cause for rupture of the membranes, toxemia, methods of induction of labor, duration of labor, presentation, methods of delivery, morbidity and complications, and infant mortality.

### Results

*Age.*—Premature rupture of the membranes occurred most frequently in the age period from 20 to 25 years. There were no patients over 40 years of age in this series.

*Color.*—In this series the distribution according to color was equal.

*Gravidity and Parity.*—There were thirty-three patients in their first pregnancy and seven additional women who had not previously borne a viable

\*Read before the Cincinnati Obstetrical Society, May 20, 1948.

vertex presentation there were 74 infants and only three deaths. All of these infants were stillborn. One had a mother with untreated syphilis, and his death occurred intrapartum. In the other two cases, the membranes had ruptured 41 and 66 hours, respectively, before the onset of labor. The birth weights were 5 pounds, 15 ounces and 6 pounds, 10 ounces, and both of the infants were macerated. Labor was not induced and it was of average duration. Delivery was spontaneous. The autopsies showed a subarachnoid hemorrhage in one infant and no conclusive findings in the other. Two infant deaths occurred among the eleven uncomplicated breech presentations. Both of these infants were premature. Labor was induced in one of these cases by Braun bag. The thirteen remaining infant deaths occurred with transverse presentations, cephalopelvic disproportion, and prolapsed cord on admission to the hospital.

There was no definite correlation between the corrected infant mortality and the length of time between the rupture of the membranes and the onset of labor, except that there was no increase in the mortality rate in instances in which the time interval was 48 hours or more.

An attempt to evaluate the results of interference was made by comparing the infant mortality in cases in which there was no attempt at induction of labor, cases in which there was induction of labor with castor oil or in a few cases castor oil with quinine, and cases in which there was bag induction. The infant mortality rate was the same with spontaneous onset of labor as with induction of labor by castor oil; it was higher in cases in which a uterine Braun bag was used for induction of labor. It was difficult to evaluate how effective castor oil was in hastening the onset of labor.

### Summary

In this series of 102 cases of premature rupture of the membranes we have found that:

1. Age, color, gravidity, and parity were not significant factors.
2. There was no increase in the incidence of pre-eclampsia.
3. There was no history of trauma or other apparent cause for rupture of the membranes.
4. There was an increased incidence of malpresentations, cephalopelvic disproportion, and prolapsed cord.
5. The time interval between rupture of the membranes and the onset of labor ranged from less than one hour to fifty-six days.
6. The duration of labor was not increased.
7. Postpartum morbidity was not additionally prolonged when there was a long interval between rupture of the membranes and onset of labor.
8. The infant mortality was not increased with prolongation of the interval between rupture of the membranes and onset of labor.
9. The infant mortality rate was the same with spontaneous onset of labor as with induction of labor with castor oil. The infant mortality was higher when labor was induced by uterine insertion of Braun bag.
10. The total infant mortality was high, but in uncomplicated cases it was only slightly above average.

The period of this study in part antedated the employment of prophylactic chemotherapy, which is now routine.

*Maternal Mortality.*—There was one death in this series. The cause of death was lobar pneumonia, post partum, and the patient died on the eleventh post-partum day. Her membranes had ruptured 24 hours before onset of labor.

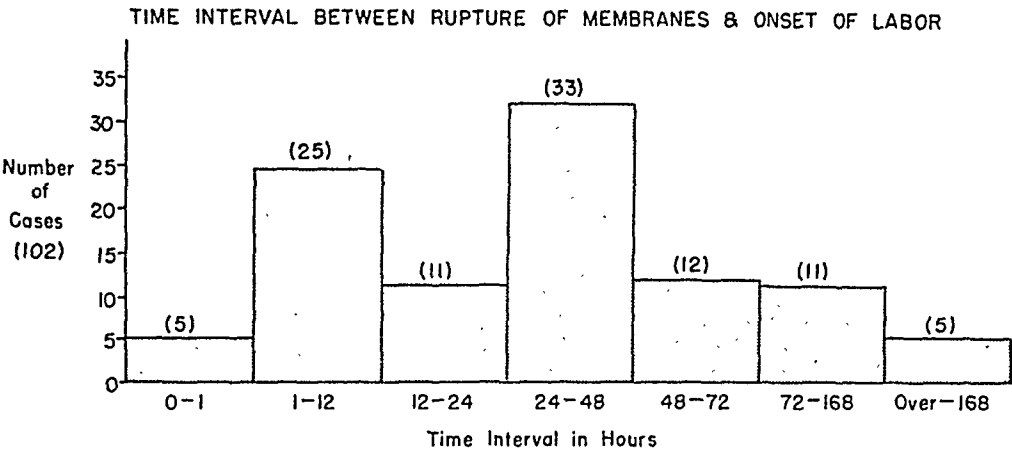


Fig. 1.

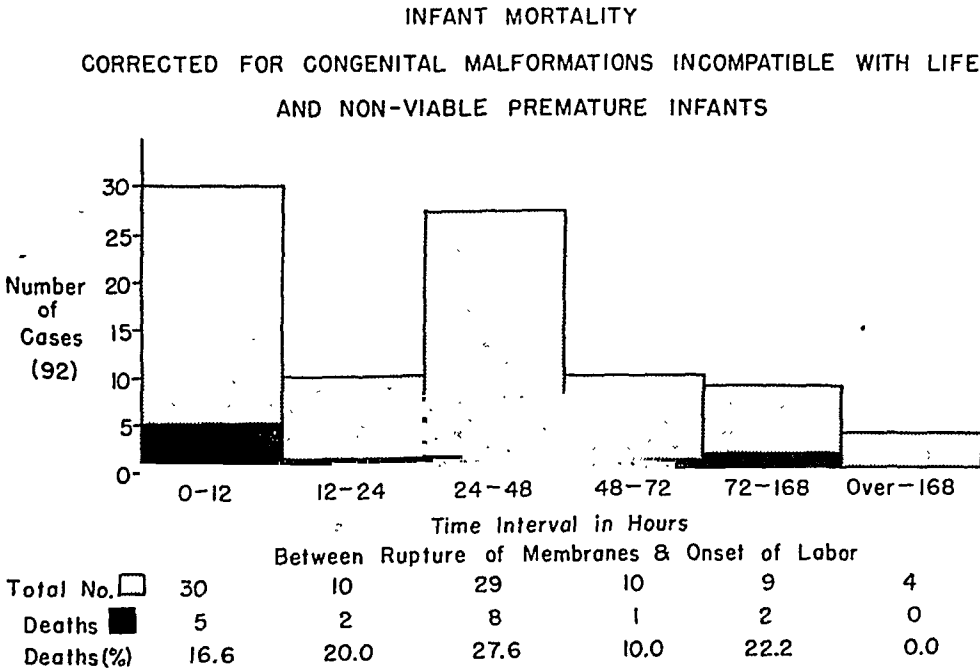


Fig. 2.

*Infant Mortality.*—The uncorrected infant mortality was 30 out of 104 infants, or 28.8 per cent. Making corrections for nonviable premature infants and for congenital malformations incompatible with life, the mortality was 18 out of 92 infants, or 19.6 per cent. There were 65 infants in the series whose birth weight was over 2,500 Gm. (5 pounds, 8 ounces), and 39 infants whose birth weight was 2,500 Gm. or less. Twelve of the infant deaths occurred in the former group. A breakdown of the infant mortality was made into the uncomplicated group and into the group composed of transverse presentation, prolapsed cord, and cephalopelvic disproportion. In the group of uncomplicated



## THE RELATIONSHIP BETWEEN THE HEMORRHAGIC BLOOD DYSCRASIAS AND HYPERMENORRHEA

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THAT the hemorrhagic blood dyscrasias may be associated with hypermenorrhea is recognized,<sup>1, 2</sup> and excessive menstrual flow may well be the presenting symptom in women whose final diagnosis is thrombocytopenic purpura.<sup>3</sup> The mechanism of this relationship remains uninvestigated, however, it having been generally assumed that uterine bleeding is controlled by the same mechanism by which rhexis in general is controlled.<sup>4</sup> Crossen and Crossen exemplify this assumption when they state that "uterine bleeding may be due to the condition of the blood without any local disease."<sup>2</sup> The opportunity during the past three years to see, in consultation, a considerable number of women with hematologic problems<sup>5</sup> has convinced the author of the incorrectness of this statement; and the present report suggests a possible mechanism by which the patient with hemorrhagic tendencies may acquire hypermenorrhea. The studies recorded are based on (a) menstrual blood loss measurements in patients whose clotting mechanism was artificially altered, (b) a survey of the histories of women suffering from hematologic disease with bleeding tendencies (thrombocytopenic purpura, aplastic anemia, etc.), and (c) a review of the pelvic findings, both gross and histologic, in a series of such patients.

*A. Blood Loss Measurements.*—Under normal circumstances menstrual blood has no clotting mechanism,<sup>5</sup> and would possibly be unaffected by alterations in the circulating blood coagulability. Furthermore, it has been demonstrated that the other physiologically nonclotting form of uterine blood, postpartum blood, is not increased in amount by hemorrhagic tendencies in the peripheral blood.<sup>6</sup> Accordingly, blood loss measurements, using the method previously described,<sup>7</sup> were carried out on each of six women through two consecutive menstrual periods.

With each patient one of the two periods was considered the control (the first in five of the cases, the second in one); during the other period the patient received anti-coagulant medications. In three of the subjects, dicumarol was started forty-eight hours prior to the expected onset of flow, and the prothrombin level held below 20 per cent for at least two days of the period. In the remaining three patients heparin was administered and the clotting time raised above twenty-five minutes for at least thirty-six hours of the period. In no patient was there a substantial increase of flow during the treated period, and averaging the groups, the blood loss for the treated and the control periods was approximately identical. There was, in other words, no immediate increase in amount of blood lost reflecting these particular alterations in clotting mechanism.

*B. The Histories.*—The records of 200 patients with hemorrhagic blood dyscrasias were reviewed. Of these, 61 were women within the menstrual years

\*The author wishes to express his appreciation to the members of the Kinsman Hall Hematology Clinic for their cooperation in making patients available for this study.

### Conclusions

This survey shows that in cases of premature rupture of the membranes without other complications conservative treatment is indicated. The patient should be hospitalized, spontaneous onset of labor should be awaited or a medical induction with castor oil may be allowed, and there should be no interference with normal labor. Chemotherapy may be administered as a prophylactic measure.

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Actually there were more pelvic lesions than there were patients who had presented a history of menstrual abnormality, but the point of interest is that every patient with such a history had a pelvic lesion which could have been held accountable for her hypermenorrhea.

*Current Cases.*—Through the courtesy of Drs. Charles A. Doan and Bruce K. Wiseman, it has been possible for the past year and one-half to perform a dilatation and curettage at the time of splenectomy on all women in the menstrual years with thrombocytopenic purpura and associated hypermenorrhea. Combined with this, the pelvis has been explored manually from within the abdomen at surgery. Seven patients have been so examined and in an additional three cases it has been possible to obtain pathologic material from gynecologic operations performed elsewhere after the onset of symptomatology but prior to the patient's registration at this hospital. In the three patients operated upon elsewhere, chocolate cysts of the ovaries were encountered in one case, an old tuboovarian process in one, while in the third patient sections of the removed uterus revealed a marked hyperplasia of a nonsecretory endometrium in an otherwise normal-appearing organ. The findings in the seven patients seen in this hospital are recorded in Table II. Two of these patients (No. 2 and No. 3) are still under therapy for mild hypermenorrhea, the splenectomy having corrected the blood picture and purpuric tendency but not the excessive menses.

TABLE II

PATIENT	ENDOMETRIUM	UTERUS	TUBES	OVARIES
1	Swiss cheese hyperplasia	Large normal	Negative	Unilateral chocolate cyst
2	Interstitial hyperplasia	Normal	Old pelvic inflammatory disease	Multiple small unruptured follicles
3	Interstitial and glandular hyperplasia	Multiple fibroids	Negative	Negative
4	Interstitial hyperplasia	Large, congested	Old pelvic inflammatory disease? Old tubal hemorrhage?	Negative
5	Normal nonsecretory	Normal	Negative	Bilateral chocolate cysts
6	Swiss cheese hyperplasia	Normal	Active tubal bleeding bilateral	Tuboovarian mass on left
7	Glandular hyperplasia	Normal	Negative	Normal size. Not visualized.

### Discussion

To assume that alterations in the clotting mechanism of the circulating blood lead directly, without any local disease, to hypermenorrhea, commits one to the converse proposition that in a normal woman the duration and amount of menstrual flow is a function of the coagulability of the peripheral blood. In general, it has been felt that in normal women both the duration and the amount of menstrual flow have an endocrine control.

It is not the purpose of this paper to attempt to demonstrate in detail the etiologic relationship between the various pelvic findings encountered and hypermenorrhea. Admittedly, the morphologic findings in bleeding patients are often tenuous as etiologic explanations, and in cases of functional bleeding consist most often of hyperplasia of a nonsecretory endometrium which presumably reflects an endocrine imbalance. But it should be stressed that any one of the

(13 to 50). One patient had originally presented herself at the Gynecology Clinic with fibroids, and her record is not considered here. Of the remaining patients, twelve had or had had marked hypermenorrhea. Considered alone, these figures are not significant, since they must be compared to the average incidence of hypermenorrhea in the clinic population. As a control group, therefore, 60 consecutive women in the same age range who had registered in the Medical Out-patient Department were considered. Six of this group of patients had or had had a history of hypermenorrhea. These figures are summarized in Table I, and indicate that a history of hypermenorrhea is twice as frequent in the hemorrhagic blood dyscrasias as in the average clinic population.

TABLE I

	WOMEN IN MENSTRUAL AGE	NUMBER WITH HYPERMENORRHEA	PER CENT
Thrombocytopenic purpura	45	11	
Aplastic anemia	15	1	
	<u>60</u>	<u>12</u>	20
Medical Out-Patient Department	60	6	10

In reviewing these records, four cases were found in which ovarian irradiation or surgical castration had halted the excessive menstrual flow, although the hematologic picture remained unchanged, and the patient continued to manifest purpuric symptoms elsewhere. This would indicate that the excessive menses of the patient with hematologically caused bleeding tendencies may not be entirely analogous in its mechanism to the generalized purpuric manifestations.

Finally, one must be concerned about the 80 per cent of patients with hemorrhagic blood dyscrasias who did not display any alteration in their regular menstrual history. If the hypermenorrhea is explained simply on the grounds that the blood circulating through the uterus possesses a clotting defect, it would be reasonable to expect it to be, like the purpuric spots on the skin, an almost universal symptom. Some additional factor, other than the blood disease per se, must contribute the difference between those women who suffer excessive menstrual flow and those who do not.

*C. The Pelvic Status.*—Information as to the pelvic status of these patients was obtained from two sources: a review of postmortem material and an investigation of current cases.

*Postmortems.*—Material was available in the files of the Department of Pathology from 35 patients. These were women between the ages of 13 and 50 years in whom the history was adequate from the gynecologic point of view. In this particular group were included the leukemia patients as well as those with thrombocytopenia and aplastic anemia. Two of these patients had previously had hysterectomies, and of the remaining 33, ten had a history of a definite and substantial increase in menstrual flow. A review of the pathologic material in these 33 cases revealed the following pelvic entities:

Leucemic infiltration (myometrium or endometrium)	5
Fibroids	4
Endometrial polyps	2
Endometrial polyps and fibroids coexisting	1
Subendometrial hemorrhage	1
Tubal hemorrhage	1
Chocolate cysts of the ovary or ovaries	2
Follicular "cystic degeneration" of the ovaries	1
Endometrial hyperplasia	8

## HETEROSPECIFIC BLOOD GROUP PREGNANCY IN HEMOLYTIC DISEASE OF THE NEWBORN\*

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**R**EPORTS on isoimmunization during a heterospecific blood group pregnancy by the A and B agglutinogens are relatively rare in comparison with the vast number of publications dealing with the immunizing process by the RII factor.

A review of the literature emphasizes confusion which exists over many questions in relation to this problem. All authors now agree that congenital hemolytic disease of the newborn due to A-B sensitization usually takes a milder course with frequent spontaneous recovery than that due to RII-sensitization. However, severe or even fatal cases with liver damage and kernicterus also occur in cases in which the A and B agglutinogens are the basis of isoimmunization. Attempts have been made to arrive at a plausible explanation of some of its features. To analyze why isoimmunization with the A and B agglutinogens is so infrequent, the following factors have been suggested: lack of placental permeability to anti-A and anti-B; neutralization of these substances by water-soluble A and B Group substances present in the fetal plasma; lack of sensitivity of the fetal erythrocytes; and diminished activity of anti-A and anti-B at body temperature.<sup>9</sup>

Case reports on isoimmunization due to A-B sensitization are found in the American and English literature. Wiener<sup>11</sup> repeatedly mentioned its importance. The quality and quantity of an abnormal antibody, he believes, determine the varying clinical manifestations of erythroblastosis fetalis and, from this point of view, he, therefore, specifies three varieties of this disease; namely, icterus gravis, congenital hemolytic disease, and icterus praecox. The icterus praecox syndrome is commonly associated with A-B sensitization. According to Halbrecht,<sup>6</sup> icterus praecox is a milder form of pathologic icterus with minimal or no hemorrhagic manifestations. Wiener<sup>10</sup> explains the less severe character on several bases: the natural physiologic character of the a and b agglutinins in maternal sera which have in general little or no harmful effect on fetuses belonging to Groups A, B, and AB, the usually low titer of the agglutinins, and the fact that the natural isoagglutinins presumably are larger molecular aggregates which do not traverse the placenta easily.

Boorman, Dodd, et al.<sup>3, 4</sup> reported several cases. They felt that the amount of free A and B agglutinin in the fetal plasma and body fluids plays a major role in the neutralization of maternal a and b agglutinins. Other investigators<sup>2</sup> could not find an appreciable amount of group specific substances in a number of cases. Tovey<sup>9</sup> believes that the placenta exerts a definite limiting effect upon the extent to which the maternal anti-A and anti-B agglutinins can enter the baby's circulation. Polayes<sup>7, 8</sup> reported a number of cases of isoimmunization by the A and B agglutinin. Aubert<sup>1</sup> investigated one case with a remarkably high anti-A titer in a mother's serum.

\*Aided by a grant from the Newark Beth Israel Hospital Research Foundation.

patients examined in this group presented sufficient evidence to justify a diagnosis of bleeding on a strictly gynecologic basis, functional or organic, if the blood picture had not been known.

On considering the data cited above, therefore, it is suggested that: (1) a woman with hemorrhagic blood dyscrasia will not acquire hypermenorrhea without the intermediary of a local pelvic abnormality; (2) from the strictly gynecologic point of view this local finding would usually be considered sufficient to explain the bleeding organically, or to justify the diagnosis of functional bleeding of presumed endocrine cause; and (3) in most instances the local pelvic lesion itself results from the coagulation defect of the circulating blood (tubal hemorrhages, chocolate cysts of the ovary, etc.).

Essentially this would represent a reclassification of the factors to be considered in the etiology of hypermenorrhea. The hemorrhagic blood dyscrasias would not be classed as systemic causes, but as contributing to a local pelvic cause of excessive bleeding. From the immediate practical viewpoint, these tenets would re-emphasize the fact (forgotten in the patients surgically castrated prior to being seen in the Hematology Clinic) that the finding of tubal or ovarian masses in women with exaggerated menstrual flow may indicate the immediate, but not necessarily the entire etiology. Investigation of the hematologic system remains imperative.

### Conclusions

In a consideration of the relationship between excessive menstrual flow and blood dyscrasias with bleeding tendencies, it has been determined that:

1. Patients treated with dicumarol and heparin during a period showed no increase in amount of menstrual blood lost.

2. Those patients with hemorrhagic blood dyscrasias who also displayed hypermenorrhea presented sufficient evidence to justify a diagnosis of bleeding on a strictly gynecologic basis, functional or organic, irrespective of the blood picture.

In view of these findings a possible mechanism is suggested whereby the patient with hematologic bleeding tendencies acquires hypermenorrhea.

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lowing complaints: slight nausea and vomiting, occasional headaches, insomnia, and heart-burn. She was admitted to Newark Beth Israel Hospital on May 27, 1948, at 11:55 A.M. First labor pains began at 3:45 A.M. of the same day. The membranes were ruptured artificially at 12:45 A.M. and at 2:49 P.M. she delivered a premature male infant. The delivery was performed by extraction of a breech presentation and forceps application on the aftercoming head. During labor her condition was good. The placenta was delivered spontaneously a short while after. The cord appeared normal. The course of the puerperium was uneventful and she was discharged on June 6, 1948, on her tenth postpartum day.

At birth, the baby weighed 6 pounds, 10 ounces and his general condition appeared good. No anomalies were noted. There was no clinical evidence of jaundice but the cord serum showed an icteric index of 28. On the third day of life the skin became icteric and the liver and spleen were readily palpable. However, the infant remained alert, had intact reflexes, and continued to take his formula well. The jaundice increased considerably during the following days and was still discernible at the date of discharge on June 6, 1948.

The hematological findings were as follows: On May 27, 1948 (immediately after birth): red blood cells 4,830,000, hemoglobin 118 per cent, white blood cells 26,600; differential count: polymorphonuclear leucocytes 43 per cent, stabs foris 6 per cent, eosinophiles 2 per cent, myelocytes 3 per cent, lymphocytes 28 per cent, monocytes 18 per cent, nucleated red cells not noted. On the following day there was no change in these findings (red blood cells 4,890,000; hemoglobin 112 per cent). On May 29, the red cell count dropped to 4,000,000 with a hemoglobin of 108 per cent and the baby was given 60 c.c. of Group O, Rh-positive blood by fontanel. On May 30, the red cell count was 3,800,000, the hemoglobin 104 per cent and another transfusion by the same route was administered. The next day (May 31) the red cell count rose to 4,730,000 and the hemoglobin to 112 per cent, and from then on the red cell count continued to climb slowly to 5,600,000 (June 5, 1948).

A serological study of parent's and infant's blood revealed: mother: Group O, RH, RH<sub>2</sub>, HR'; father: Group A, RH, HR'; baby: Group A, RH, HR'.

The mother's serum had been tested for anti-A and anti-B agglutinins as follows:

*January 14, 1948, 3rd month:* anti-A 1:256, anti-B 1:8.

*May 16, 1948, 8th month:* anti-A 1:512, anti-B 1:8.

*May 29, 1948, 2 days post partum:* anti-A 1:1024, anti-B 1:8.

No maternal anti-A agglutinins could be detected in the infant's serum. The infant's serum was also tested for A and B group substances. For this purpose equal parts of infant's serum and maternal serum were mixed, incubated for 2 hours in a water bath at 37° C., and then titrated against A and B cells. At the same time the untreated maternal serum was titrated against the same cells. These tests yielded the following results:

*Maternal serum:* anti-A 1:1024, anti-B 1:8.

*Infant's serum:* anti-A none, anti-B none.

*Maternal serum mixed with infant's serum:* anti-A 1:256, anti-B 1:4.

Since the maternal serum was diluted with the infant's serum in a proportion of 1:2, the titer of the treated serum had to be multiplied by 2, so that the final reading was: anti-A 1:512, anti-B 1:8.

The inhibiting index of the infant's serum is computed by dividing the agglutination titer of the untreated serum by that of the treated serum:

$$\frac{1024}{512} = 2 \text{ Inhibition Index}$$

This experiment performed on the sera of Case 1 showed no inhibiting properties of the fetal serum whatsoever.

### Discussion

From the serological point of view these two cases present a pronounced difference in titer between the a and b iso-hemagglutinins. An outstanding finding was the excessively high anti-A titer in Case 1 and the comparatively low anti-A titer in Case 2. Usually the newborn possesses at birth no agglutinins of

## Case Reports\*

CASE 1.—Mrs. A. F., 28 years old, white, four years married, a para i, gravida ii, with a history of death of her first child one year ago. Death occurred after twenty-four hours and a postmortem examination revealed a large interventricular septal defect of the heart.

She was now admitted on March 11, 1948, at 11 P.M. First labor pains began at 9 P.M. and at 2:55 A.M. of the following morning she delivered spontaneously a full-term male infant in right occipito anterior position. Her condition during labor was good. The placenta was expelled spontaneously. The cord appeared normal. The puerperium was uneventful and she was discharged on March 19, 1948, on her eighth postpartum day.

The infant appeared well developed and weighed 8 pounds at birth. However, his general condition was poor. Respiration was labored, the cry weak, and the airways appeared filled with mucus. The skin was of a pronounced pallid color and the face showed marked edema. The heart sounds were good and no murmurs could be heard. The abdomen presented no unusual signs. Liver and spleen could not be palpated. The question of a possible cerebral hemorrhage or a congenital heart lesion was raised by the pediatrician.

The laboratory findings were as follows: red blood cells 3,560,000, white blood cells 35,750, hemoglobin 80 per cent; differential count: polymorphonuclear leucocytes 41 per cent, stab foris 32 per cent, eosinophiles 2 per cent, basophiles 1 per cent, myelocytes 2 per cent, lymphocytes 16 per cent, monocytes 6 per cent; 86 nucleated red cells per 100 white blood cells.

A serological study of parent's and infant's blood revealed the following: mother: Group O, RH<sub>1</sub> hr'; father: Group A, rh HR'; baby: Group A RH<sub>1</sub> HR'.

It was evident that two incompatibilities were present; one between the main blood groups, the other in the HR-factor. No HR-antibodies could be detected in the maternal serum, either in saline or in albumin media. (Tests were performed in both AB-plasma and bovine albumin.) A series of 30 Group O rh-negative cells was used. However, the serum, when tested for anti-A and B agglutinins, revealed an abnormally high anti-A titer. This titer determined by several methods and rechecked repeatedly was found to be 1:200,000, while the reading of the anti-B was never higher than 1:200. Group A and group B cells with all available varieties of the RH-agglutininogen were tested under 22° and 37° Centigrade. Optimum agglutination was best obtained under room temperature (22° C.), while no pronounced deviation in titer could be detected between saline and albumin media. The infant's serum revealed the presence of maternal anti-A agglutinins up to dilutions 1:2 in saline and 1:8 in albumin media. Both maternal and infant's sera were tested 12 hours and 3 days post partum.

On the basis of these findings the diagnosis of erythroblastosis fetalis was made and the baby transfused immediately, by fontanel, with 60 c.c. of Group O RH-positive blood. The baby also received continuous oxygen, caffeine, and other symptomatic treatment.

The following day, on March 13, the red cell count rose to 4,690,000, the hemoglobin to 110 per cent; on March 14 and 15, the count declined to 3,890,000 (Hgb. 103 per cent), slight jaundice was noted, and the baby was transfused again. The following day, on March 16, the red cell count rose to 5,310,000 and the hemoglobin to 110 per cent, and remained at this level.

The further course was uneventful. On March 27, the baby showed the following blood picture: 5,300,000 red cells; hemoglobin 102 per cent; 9,800 white cells; polymorphonuclear leucocytes 39 per cent; stabs 5 per cent; lymphocytes 55 per cent; monocytes 1 per cent; and absence of nucleated red cells. Maternal anti-A agglutinins could no longer be detected. The baby was kept under observation until April 2, 1948, on which day he was discharged. At the present time the child is living and well.

CASE 2.—Mrs. R. L., 36 years old, white, para 0, gravida ii, had one spontaneous miscarriage at 18 weeks' gestation in 1947. During her second pregnancy she had the fol-

\*We are grateful to Dr. David Gershenfeld and Dr. L. E. Savel for the use of the clinical material.



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his own, and any agglutinins demonstrable in his serum are those of his mother which have filtered through the placenta. In Case 1 maternal a and b agglutinins penetrated the placental barrier and were readily demonstrated in the fetal serum in measurable quantities. Case 1 also presented an Hr-incompatibility without demonstrable Hr-anti-bodies, a factor which may have contributed to such an excessive rise of its anti-A titer.

A comparison of the anti-A titer of the two cases suggests the possibility that different fractions of the A agglutigen may be responsible for such pronounced fluctuations in the serological findings. Braun and Schiff<sup>5</sup> found that the group specific substance "A" is a very complex one and consists of various protein and lipoid fractions, the latter being closely related to Forsman's antigen. That the group substance "A" plays an exclusive role in processes of isoimmunization, especially when it concerns mothers belonging to Group O, was shown by many workers in this field. Observations made on cases of Group "O" and "A" parents and Group "O" and "A" children revealed that the frequency of type A children is less in a mating with A fathers and O mothers than in cases of O fathers and A mothers; the infrequency of A children may be the result of loss by spontaneous abortion and stillbirth.

From the clinical and hematological viewpoint the first case presented a picture of erythroblastosis fetalis (congenital hemolytic disease). There was profound anemia with definite evidence of hemolysis and marked increase of nucleated red cells. At birth, the general condition of the baby was poor. Jaundice and some edema were present, but the liver and spleen were not palpable. Summarizing the findings of this case, it appears quite obvious that this infant's disease was due to isoimmunization of the mother by the blood factor "A" as demonstrated by the extremely high anti-A titer. The Hr-incompatibility may be regarded as of only minor importance because of the complete absence of any demonstrable Hr-antibodies.

The second case presented a picture similarly classified by Wiener<sup>11</sup> and described by Halbrecht<sup>6</sup> as *icterus praecox*. The infant showed an anemia with some evidence of hemolysis but no nucleated red cells. The jaundice appeared rather slowly and persisted for many days. The baby was well, nursed vigorously, was alert and had normal weight. Liver and spleen, however, were readily palpable.

### Summary and Conclusion

1. Two cases of isoimmunization of Group O, Rh-positive mothers by the "A" agglutigen are presented.
2. Enormous variations in the maternal titer may sometimes be encountered concerning the "A" agglutigen.
3. The differences in anti-A titers in isoimmunization may be due to various fractions of the "A" agglutinogens.

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The two were carefully mixed and the slide set aside for three minutes. At the end of this time the mixture was observed until a six-minute period had ended. Care was taken to prevent too vigorous agitation and breaking of the clumps which makes a positive test appear negative. All of the slides were read with oblique lighting against a white background. In the positive test clumping was always clearly visible in six minutes, at which time all observations were terminated. The slide method using human sera (glutinin test) was performed by placing two drops of oxalated blood on a clean slide at 70° F. One drop of the Anti Rh<sub>0</sub> serum was added and the mixture spread over the slide. The slide was placed over a viewing box and rotated back and forth. Clumping was designated as Rh<sub>0</sub> positive. The test was terminated in two minutes. The test tube method was done by mixing one drop of Anti Rh<sub>0</sub> serum with a drop of 2 per cent fresh blood suspension in a small narrow test tube. This was incubated at 37° C. for one hour and the reaction read grossly by inspecting the sediment in each tube. The tube was rotated at an angle in order to separate the sediment from the bottom of the tube. The tubes were allowed to stand one hour at room temperature and then read macroscopically.

### Results

A total of 1,000 Rh<sub>0</sub> factor determinations were done at random. In this series 150 (15 per cent) were Rh<sub>0</sub> negative. In the male group, 94 (81.0 per cent) were Rh<sub>0</sub> positive and 22 (19.0 per cent) were Rh<sub>0</sub> negative. In the female group, 756 (85.5 per cent) were Rh<sub>0</sub> positive and 128 (14.5 per cent) were Rh<sub>0</sub> negative (Table I). In regard to the procedures used there is noted to be no apparent statistical differences between methods (Table II). Of the 128 Rh<sub>0</sub> negative female patients, 86 were obstetrical patients who had delivered. In this group there were eight who had babies or stillbirths with one or more of the signs of the erythroblastosis syndrome. The occurrence of the erythroblastosis factor in this series is 9.3 per cent.

TABLE I. DISTRIBUTION RH FACTOR IN AMERICAN NEGRO (CHICAGO)

REACTION TO ANTI RH SERUM*					
SEX	NUMBER TESTED	POSITIVE		NEGATIVE	
		NUMBER	PER CENT	NUMBER	PER CENT
Males	116	94	81.0	22	19.0
Females	884	756	85.5	128	14.5
	1000	850	85.0	150	15.0

\* $X^2 = 13.7$ .

P = .001.

TABLE II. COMPARISON OF ANTI RH SERUM TEST METHODS\*

METHOD	NUMBER TESTED	REACTION			
		POSITIVE		NEGATIVE	
		NO.	PER CENT	NO.	PER CENT
I Commercial serum (animal)	622	532	85.5	90	14.5
II Slide (glutinin test) (human serum)	259	221	85.5	38	14.5
III Test tube (human serum)	119	102	85.8	17	14.2
Total	1000	855	85.5	145	14.5

\*I and II  $X^2 = 1.5$

P = 0.22

n = 1.

I and III  $X^2 = 1.6$

P = 0.20

n = 1.

The short formula for Chi Square in Fourfold Tables was used.<sup>14</sup>

P value is from Fisher cited by Yule and Kendall.<sup>15</sup>

# THE Rh FACTOR IN THE AMERICAN NEGRO

## A Preliminary Report

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ONE is impressed by the abundant literature that has accumulated since 1939 on the subject of the Rh factor. Of particular interest is the racial incidence of the Rh factor and its relationship to the occurrence of erythroblastosis fetalis. The predominant amount of information available is in regard to the white population with national variations and a scant amount in reference to the Negro and Mongolian races.

Potter<sup>1</sup> has summarized most of the available material and cites the following figures: white population 85 per cent positive to the anti Rh<sub>0</sub> serum, Negro race 93 per cent positive, Mongoloid races, 95 to 99 per cent Rh<sub>0</sub> positive. Simmons et al.<sup>2</sup> in a study of 281 pure-blood aborigines found a 100 per cent Rh<sub>0</sub> positive reaction. Cole<sup>3</sup> in a recent study of 5,000 Rh determinations showed an over-all evidence of 86 per cent Rh<sub>0</sub> positive reactions. In his series 3.8 per cent (190 cases) were Negroes. Other reports on racial incidence from 1943 to 1946 have been tabulated by Potter.<sup>4</sup>

The occurrence at Provident Hospital of four confirmed cases of erythroblastosis fetalis within a period of eighteen months prompted us to study the prevalence of the Rh<sub>0</sub> factor in an all Negro obstetrical unit. The availability of material may be summarized thus: admissions to the unit with delivery for the years 1945 and 1946 were 2,607. The antenatal clinic attendance for the same period was 4,378.<sup>5</sup>

### Methods of Study

1. Patients attending the antenatal clinic were typed at random for the Rh<sub>0</sub> factor and as far as possible the patient's husband was also typed.
2. Requests were made that all private patients admitted to the obstetrical service be typed for the Rh factor.
3. Individual physicians were encouraged to have Rh<sub>0</sub> factor determinations done as a routine procedure in their antenatal care. These reports were submitted at the time of admission to prevent duplication.
4. At the time of blood typing on other hospital services Rh<sub>0</sub> factor determinations were requested.
5. All cord bloods of Rh-negative mothers and those babies having any of the six cardinal signs of the erythroblastosis syndrome<sup>6</sup> were typed.

In order to increase the validity of our study and through the suggestion of Dr. Potter<sup>7</sup> three test procedures were employed: (1) commercial animal serum, (2) human serum using the slide method, and (3) human serum using the test-tube method. In the first procedure the test was performed in two steps: one, the preparation of the blood suspension by carefully cleansing the finger, pricking it with a fine bistoury, and dropping two full drops of blood into 0.5 c.c. of a buffered normal saline solution containing 1 per cent sodium citrate; second, the placing of one drop of the cell suspension on a clear glass slide at 70° F., placing next to this one drop of commercial anti-Rh<sub>0</sub> serum.

in our present series. No available data to date have been received on the occurrence of erythroblastosis in their series.

Since the initiation of this study we have done approximately 2,700 additional Rh<sub>0</sub> determinations. In this data, as in the previous data, there was the same range with the standard deviation being less than  $\pm 1.5$ . These analyses will be reported in a future paper.

### Summary

1. One thousand Negroes were tested at random for the Rh<sub>0</sub> factor. In this series 15.0 per cent were Rh<sub>0</sub> negative, a figure that corresponds with that of the Caucasian population.

2. Three test procedures were employed and one statistical variation was noted.

3. The blood groupings were noted to be of the normal distribution found in the general Negro population.

4. The incidence of the erythroblastosis factors in this series was 9.3 per cent.

5. A brief discussion of racial characteristics is included and a comment made on routine Rh<sub>0</sub> factor typing.

The authors wish to acknowledge the technical assistance of Mr. Walter L. Turner and Mr. Randolph Hughes.

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There can be no definite statement made as to the correlation of the blood groupings and the presence or absence of the Rh<sub>0</sub> factor. The high incidence of the O type blood is in keeping with the distribution of O typed blood in the general Negro population. The remaining blood types are of normal distribution. It is interesting to note the correlation of the blood types with the data of Wiener<sup>8</sup> on tests of 500 Negroes (Table IV). With this specific correlation there may be justification in postulating that the incidence of Rh<sub>0</sub> factor is lower in the American Negro seen in the semi-private clinics of the Chicago area than in areas previously studied.

TABLE III. TESTS WITH ANTI RH<sub>0</sub> SERUM ON THE AMERICAN NEGRO

INVESTIGATORS	NO. TESTED	PERCENT RH-POSITIVE	PERCENT RH-NEGATIVE
Landsteiner and Wiener <sup>11</sup>	113	92.0	8.0
Levine <sup>12</sup>	264	95.5	4.5
Tisdale and Garland <sup>13</sup>	283	91.2	8.8
Authors	1000	85.5	14.5

TABLE IV. RH FACTOR DISTRIBUTION WITH BLOOD TYPE (PER CENT) \*

NO. TESTED	RH FACTOR	O	A	B	AB
743	Present	59.2	22.8	13.2	4.8
115	Absent	33.3	36.3	27.7	2.4
500†	—	47.0	28.0	20.0	5.0

\*International Classification.

†Wiener.

## Discussion

As mentioned by Potter,<sup>4</sup> many of the studies on racial incidence have been carried out with only one type of serum and have distinguished only the presence or absence of antigens reacting with Anti-Rh<sub>0</sub> serum. In our series we used only the Anti-Rh<sub>0</sub> serum and no attempt was made to determine the existence of the various varieties of Rh antigens. In the investigation of racial origins Boyd<sup>9</sup> mentions that if data are to be reliable the character studied should not be modified by environment and should be nonadaptive and that it should be obtained by means sufficiently objective to permit exact duplication by any investigator. Potter<sup>4</sup> quotes Boyd in that, "The fundamental units of racial variability are populations and genes, not the complexes of characters which connote in the popular mind a racial distinction. Much confusion of thought would be avoided if all biologists recognized this fact. The geography of genes, not the average phenotypes, must be studied. Only a few attempts to apply this method in practice have been made to date. The most successful one among them is that concerning the blood groups in Man." These statements are well applied in this study in the determination of the Rh<sub>0</sub> factor in such a heterogeneous population as the urban northern Negro. A factor for the differential incidence in the phenotype Negro may be due to a genotypic variance characteristic of that group; this is probably due to the effects of geographic location, racial intermixture, and possibly mutations during the period of migration. In our series the use of the Bernstein formula<sup>10</sup> for racial admixture does not apply.

The importance of this study is in the consideration of transfusions and intragroups transfusion reactions and the noting that Rh<sub>0</sub> factor determinations should be done as a routine procedure.

During the course of our study, communication<sup>17</sup> with Freedmen's Hospital, Washington, D. C., reported a higher incidence of the Rh<sub>0</sub> factor than

so that it took up a left occiput posterior position. From that position the occiput was rotated manually to the hollow of the sacrum. A cephalic application was then made with the Kielland forceps to the direct occiput posterior position and with no difficulty at all the posterior occiput was rotated 180 degrees through the maternal right side to an occiput anterior position. The forceps were then replaced by an axis traction forceps and after moderately strong traction with added fundal pressure an 8 pounds 4 ounce infant was delivered. The child cried spontaneously and was in fair condition. There were no vaginal lacerations other than the mediolateral episiotomy which had been done in the perineal phase. The infant had a transient unilateral facial weakness, otherwise was normal. Both mother and baby were discharged on their ninth postpartum day after an uneventful hospital course.

In this case (Fig. 1) the back was clinically posterior and to the right whereas the occiput was to the left; this required rotation first to the hollow of the sacrum and then anteriorly through the maternal right or opposite side.

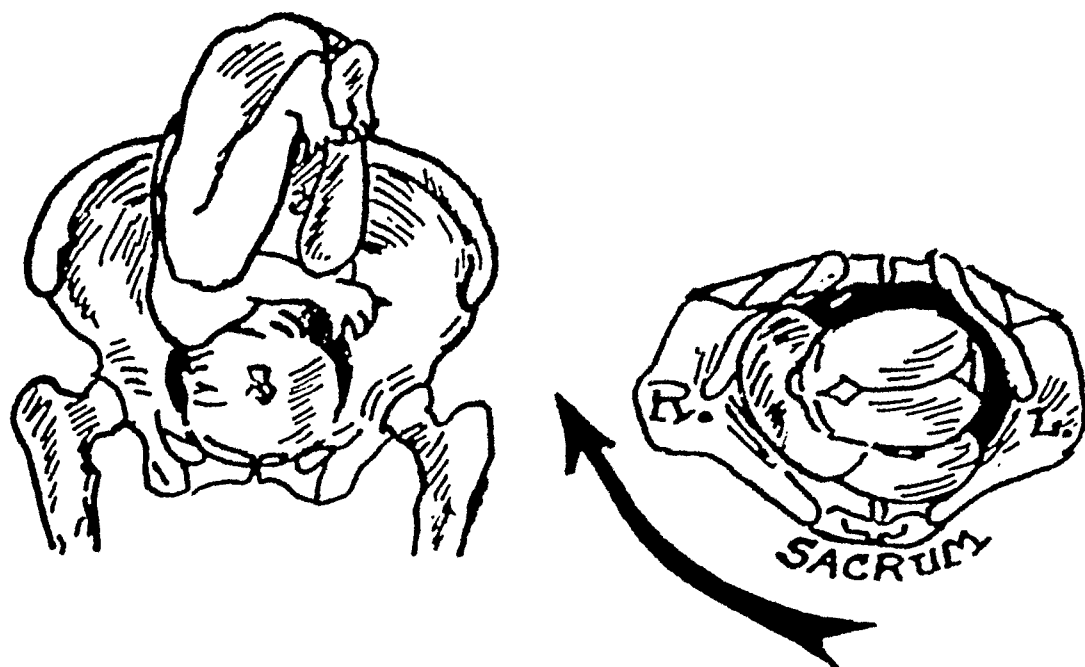


Fig. 1.—Vertex presenting in left occipitotransverse position, fetal back occupying the right posterior oblique. Arrow shows direction of successful rotation toward the fetal back.

CASE 2.—L. G., a 22-year-old gravida ii, para i, with a previously normal labor history and a normal antepartum course, was admitted to the hospital on March 19, 1948. Her expected date was March 15.

The patient experienced a mild desultory first stage of fourteen hours' duration. After a one-hour second stage the patient was examined in the delivery room and the diagnosis of a persistent right occiput posterior position in low midpelvis was made. Thickness of the abdominal wall was such as to make identification of the small parts impossible. The fetal heart was on the right side.

A cephalic application was made to the right occipitoposterior position with the Kielland forceps. With adequate available anterior-posterior space, attempt was made to dislodge the head upward to effect rotation at a higher level. This attempt was met with sufficient resistance to warrant its abandonment. Attempt to rotate at the level of arrest to a right occipitoanterior was also met with considerable resistance. The forceps were then removed and the previously diagnosed position was checked and found to be correct. The forceps were then reapplied as before and the occiput rotated to the hollow of the sacrum. In this position traction was applied in an attempt to deliver it as a direct occiput posterior. Here again moderately strong traction failed to advance the head. After consideration,

## THE ROLE OF THE FETAL BACK IN ATYPICAL OCCIPUT POSTERIOR POSITIONS\*

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IT HAS long been recognized that posterior and transverse positions of the occiput at the onset and during labor do not represent deviations from normal and should not by necessity be viewed with concern.

Failure of rotation of these initial positions caused by either faults of the maternal pelvis, soft parts, or labor result in persistent posterior or transverse positions which may spell more difficulty for the mother, the obstetrician, or both. The difficulties thus experienced have been variously ascribed to the larger cephalic diameter necessary for passage, the lack of flexion, and the inefficient direction of drive. In addition, it is often highly significant that the very faults in the maternal pelvis which contribute to the persistence of these positions are frequently etiologically significant in their manifest difficulties.

To these should be added another factor which deserves further elaboration: that is, namely, the fetal back. The importance of this was fully recognized by Pomeroy many years ago in describing his technique of manual rotation. In the following two cases, attempt will be made to demonstrate that the position of the fetal back may be of considerable significance in persistent occiput posterior positions and that its position should be used as a guide as to the direction of operative rotation.

CASE 1.—T. K., a 25-year-old primigravida whose expected date of confinement was Jan. 29, 1942, was admitted to the hospital on February 20, roughly three weeks overdue. Early labor pains were irregular and mild so that actual labor did not start until the following day. The patient had a rather uneventful first stage of thirteen hours' duration. There was noted, however, the existence of a posterior position, presumably a left occiput posterior judging by palpation of the fontanels. On abdominal examination the bulk of the baby seemed to be on the maternal right as with marked dextrorotation and the small parts were anterior and to the left.

After a prolonged second stage the patient was taken to the delivery room where the scalp was just perceptible at the vulva and the peak of a well-molded head with a large caput was on the pelvic floor. On vaginal examination at this time, the biparietal diameter was well through the pelvic inlet and the head was arrested in midpelvis in a left occipito-transverse position. Due to the presence of moulding and caput this was checked by palpation of the fetal ears and brow. A cephalic application with the Kielland forceps was made by wandering the anterior blade into position rather than in the classical manner. Traction was applied in the transverse position in order to bring the head to a lower level for rotation. This was met with considerable resistance and rotation anteriorly could not be accomplished at either above or below the level of arrest.

The forceps were then removed and the accuracy of the previously diagnosed position was rechecked and found to be correct. Suprafundal pressure was then applied and it was observed that with pressure the occiput tended to rotate toward the hollow of the sacrum

\*Read before the New England Obstetrical and Gynecological Society, May 5, 1948.



From the study of these two cases and on consideration of purely mechanical principles, it would seem evident that the fetal body and back exert a very decided effect not only on success but also on the direction of rotation of the occiput. A frequent observation in spontaneous deliveries is to see the occiput restitute after delivery 135 degrees to the oblique posterior position. We must assume then that the back had failed to rotate with and accompanying the head. Thus we know that the occiput can and does frequently rotate 135 degrees on the back without cervical or brachial injury. In spite of this, an external attempt to rotate the anterior shoulder to accompany the rotation of the occiput is mechanically sound. Due to the anatomy of the cervical spine and the brachial plexus attempts to rotate the occiput on the back beyond 135 degrees may result in irreparable damage to the fetus.

In view of this it is of utmost importance to recognize the position of the fetal back before embarking upon any operative rotation. This is especially important when the occiput is directly posterior in the hollow of the sacrum, in which case the back may occupy either the right or left oblique posterior position. The fetal heart is not a reliable indicator since in such positions it may be heard on either side depending on whether it is transmitted through the back or through the anterior chest.

If on account of thickness of the abdominal wall or for other reasons the fetal back cannot be definitely outlined, palpation of the fetal head while fundal pressure is being exerted from above may give the clue as to the direction of rotation. If these measures should fail, and in any event, rotation should be carried out with such gentleness as to detect an abnormal resistance encountered which might indicate a torsion of the infant's neck beyond safe anatomical limits.

### Summary

1. Two cases of occiput posterior positions are reported in which the occiput occupied the opposed side of the maternal pelvis from the fetal back.
2. Successful rotation in each case described an arc greater than 180 degrees toward the side of the fetal back.
3. The importance of recognizing the position of the fetal back before embarking upon operative rotation is emphasized.

The author acknowledges with appreciation the preparation of the accompanying illustrations by Dr. Gilbert Heublein.

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an attempt was made to rotate the head from its present direct posterior position through 180-degree arc on the left side of the maternal pelvis. With great ease and with no undue force this was accomplished and the occiput brought anteriorly to the symphysis. An 8 pound, 2 ounce infant in good condition was then delivered through the outlet without difficulty following a mediolateral episiotomy. Restitution occurred 135 degrees to the left side to the left occiput posterior position. There were no vaginal lacerations. Both mother and infant were discharged from the hospital on their sixth postpartum day in good condition after an uneventful hospital course.

In this case (Fig. 2) the direction of finally successful rotation plus the direction of restitution leaves little doubt that the back occupied the left posterior oblique position while the occiput occupied the right posterior oblique position. This required rotation first to the hollow of the sacrum and then anteriorly through the maternal left or opposite side.

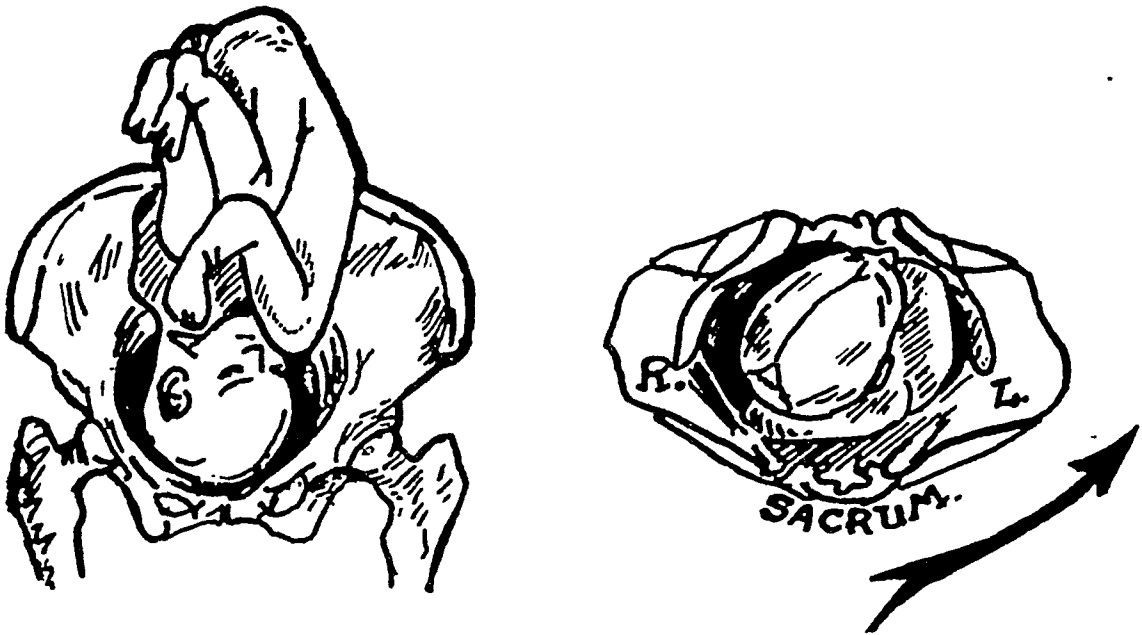


Fig. 2.—Vertex presenting in right occipitoposterior position, fetal back occupying the left posterior oblique. Arrow shows direction of successful rotation toward the fetal back.

### Discussion

These two cases represent situations in which, by virtue of torsion of the infant's neck, the occiput and the fetal back were on opposite sides of the maternal pelvis. It is felt that this condition is not as uncommon as experience would lead one to believe and that it may be the cause of some cases of failure of rotation which have often been handled by internal podalic version or other means.

The possible mechanism of this torsion is rather difficult to understand. It seems logical to suppose that probably at the onset of labor the occiput and fetal back were in alignment. During labor, as is not uncommonly the case, the occiput probably rotated to the hollow of the sacrum. With further progress of labor changes in flexion may have occurred which brought the occiput to a more dependent position and thus started its anterior rotation but in the opposite direction. This line of reasoning can be considered only speculative in character.

## Literature

Borst-Würzburg<sup>2</sup> is credited with describing, in 1904, a lesion of the type under discussion, which affected the skin. Schiller<sup>3</sup> gave credit to Schottländer and Kermauner who reported, in 1912, observations of conditions of the uterine cervix similar to those described, and Schiller<sup>4</sup> himself, in 1936, reported a study of serial sections of all cervixes brought to the laboratory where he worked. He felt that stages in the process of formation of cancer of the uterine cervix could be identified, the first and earliest stage being that known as the "carcinomatous zone" stage, wherein invasion or penetration of the so-called basement membrane had not occurred. This superficial lesion could spread within the surface epithelium to various degrees. In more advanced stages there would be some localized invasiveness and in a third stage the process would be further extended.

Such investigators as Telinde,<sup>5,6</sup> Novak,<sup>7</sup> Martzloff,<sup>8</sup> MacFarlane,<sup>9</sup> and their associates, and more recently Meigs<sup>10</sup> and Ayre<sup>11</sup> have published conjectures as to causation of processes of this type. These early lesions might be considered to be smoldering cancers which potentially are destructive.

## Survey of Cases and Results of Follow-Up Investigation

I wish to report a survey of thirty-two cases of early lesions of the sort here under consideration, encountered at the Mayo Clinic from 1932 to 1946, inclusive (Table I).

TABLE I. PARTIAL SUMMARY OF CASES

Material	Year of diagnosis	1932	1936	1940	1941	1942	1943	1944	1945	1946	TOTAL
	Number of patients	1	1	2	5	2	4	6	6	5	32
	Age of patients, inclusive years	20-29		30-39		40-49		50-59		60-69	32
	Number of patients	5		8		12		6		1	
Relevant symptoms, history, and signs	Chief complaint relative to pelvis, patients				Present			Absent			32
					18			14			
	History of bleeding, patients				12			20			32
	Previous pregnancy, patients				27			5			32
	Pelvic treatment previous to year of diagnosis, patients				8			24			32
	Cervical lesion	Erosion	Polyps	Leuco-plakia	Cystic change	Normal	Not recorded	32			
	Patients, number	16	7	2	4	1	2				
Diagnosis	Biopsy	In office, plus cauterization			In office, biopsy only		In operating room			32	
	Patients, number	14			4		14				
	Squamous-cell epithelioma grade	1		2		3		4			32
	Patients, number	1		4		24		3			
Definitive treatment	Type of treatment	Abdominal hysterectomy	Vaginal hysterectomy		Dilatation curettage and radiation			None at clinic <td rowspan="2">32</td>			32
	Patients, number	19	9		3			1			

In May, 1947, a survey of the records to include 1946 was made, and the findings were deduced from the records of a recent physical examination or

## CARCINOMA IN SITU OF THE UTERINE CERVIX\*

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IN 1932, Dr. A. C. Broders<sup>1</sup> gave the term "carcinoma in situ" to a type of epithelial lesion, clinically not malignant, sometimes found by the microscopist in removed tissue. Broders' term is clearly descriptive. The same lesion has been designated as "intraepithelial cancer," "pseudomalignancy," "precancerous lesion," "epithelial restlessness," and "covert cancer."

Broders said of "carcinoma in situ" that it is a condition in which malignant epithelial cells and their progeny are found in or near the positions occupied by their ancestors. The carcinomatous cells have not penetrated the so-called basement membrane. In this condition, moreover, the cells which have undergone malignant change have not migrated. If such migration had taken place, it would be manifested by the cells having entered the connective tissue interstices or any part of the blood or lymph vascular system.

The superficial malignant change which is the subject of this article occurs at, or distally adjacent to, the area where the squamous and columnar epithelium meet at the external uterine orifice. It is, then, adjacent to the secreting columnar cells of the endocervix. In this region, the alkaline intrauterine secretions probably are in their greatest concentration. It is here, furthermore, that the alkaline intrauterine secretions are first subjected to the acidifying and liquefying action of the vaginal fluid.

The lesion seems to involve primarily the squamous, protecting or covering epithelium. It may be so tiny as to be entirely removed by an ordinary nasal punch when this instrument is used to remove a specimen for biopsy or it may extend laterally over the portio vaginalis to involve an adjacent portion of the vaginal wall.

Various pathologists have found, in this early lesion, abnormalities in size of cells, abnormalities in size and staining qualities of the cell nuclei and a jumbled arrangement of cells. However, the cells do not seem to have possessed the property of invasiveness. The aberrations listed suggest loss of strength or softening of the extracellular framework. The foregoing phenomena stimulate speculation as to the process which caused this distortion and these cellular changes. Did some intracellular force cause the framework to give way; did some extracellular disruptive substance fail to be inhibited? Was the morphologic cellular change due to intracellular or extracellular alteration? At all events, an abnormal and seemingly uncontrolled growth is a predominant characteristic of cancerous tissue.

\*Read at a meeting of the Minnesota Society of Obstetrics and Gynecology, Rochester, Minn., May 1, 1948.

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from a questionnaire. The interval between May, 1947, and the date of definitive treatment varied widely. In nine cases the interval was one year; in six cases, two years; in six cases again, three years; in two cases, four years; in five cases, five years; in one case, seven years; and in another case, fifteen years. Two patients had died of heart disease but in no case had carcinoma recurred.

In Table I it is recorded that in fourteen cases a specimen for biopsy was removed in the office and cauterization was performed. In eight of these cases carcinoma was not found later in the surgically removed cervix. In Table I, also, the notation appears that a specimen for biopsy was obtained in the operating room in fourteen cases. In four of these, no carcinoma was found in the remaining tissue which was removed at hysterectomy. Of these four cases, conization had been performed previously in two, in one at the clinic and in one elsewhere; the removed specimen was forwarded to the clinic for examination by a pathologist. In one of the four cases, a Sturmdorf operation previously had been performed elsewhere; again the removed specimen was submitted and the diagnosis confirmed at the clinic. In the remaining case of the four, the surgeon at the clinic evidently had included all of the carcinoma in the portion he removed for biopsy.

### Comment

In the five years, 1940 to 1944, inclusive, 739 cases of carcinoma of the cervix were encountered at the clinic, including nineteen cases of carcinoma in situ, an incidence of 2.57 per cent of all cases of cervical carcinoma encountered in the five years. In this same five years, as an office procedure, approximately 1,600 cervical specimens were taken for biopsy, in eleven of which carcinoma in situ was found, an incidence of 0.68 per cent. The period of five years was taken for this part of the study because over-all figures for incidence of cervical carcinoma were available for that period.

In the entire period of fifteen years, during which the thirty-two cases of this series were collected, in eighteen the diagnosis was based on tissue removed for biopsy as an office procedure. Of these eighteen cases, in fourteen the cervix was cauterized, also as an office procedure. When these fourteen patients subsequently underwent total hysterectomy, the cervixes of eight were free of carcinoma, whereas some carcinomatous tissue remained in the cervixes of the other six. The remaining four patients of the eighteen were not subjected to cervical cauterization in the office. Of these, three underwent total hysterectomy and carcinomatous tissue was found in the removed cervixes. The remaining patient of the four refused to undergo hysterectomy and she has not been heard from since.

All consultants of the Department of Obstetrics and Gynecology contributed to the foregoing statistics. All, furthermore, concur in finding nothing diagnostic of carcinoma in the clinical appearance of cervixes in cases such as are considered herein. The importance of this article, finally, is that it points out how valuable and perhaps lifesaving an act it may be for the gynecologist to take a specimen for biopsy from any cervix of abnormal appearance, even if that appearance does not suggest to him the presence of carcinoma.

After five days this dosage was reduced to 50 mg. orally three times daily until they were well into the fourth month of pregnancy, when it was discontinued. They are still progressing normally, now in the sixth month of pregnancy.

Eight cases were classified as plus 3 (nauseated all day long and vomiting three or four times daily). These patients were given 50 mg. intravenous Benadryl four times the first day, which stopped the vomiting in each case, and then 100 mg. Benadryl or Histadyl orally three times a day until all nausea ceased at which time they were instructed to reduce the dose gradually as their symptoms permitted. Most of them were able to reduce the dosage to 50 mg. twice daily within a ten-day period and keep symptom free on that small dosage, leaving it off entirely by the time they entered their second trimester.

Twelve cases, at about six or seven weeks' gestation, were classified as plus 2 (nauseated all day long and vomiting from none to two times daily). These patients were given Benadryl or Histadyl in 50 mg. doses three times a day and told to double the dose if they needed it. Eleven were totally relieved within three days. The other patient was partially relieved but an increase in the dose caused dizziness and drowsiness of which she complained more than the nausea. She was tried on both drugs but the side effects were the same. She was given 100 mg. pyridoxine hydrochloride intravenously three times a week for two weeks following which time she was placed on 50 mg. Histadyl at bedtime and after three weeks of this therapy, having been maintained symptom free save for occasional morning nausea, the drug was discontinued.

Six cases, of four to seven weeks' gestation, were classified as plus 1 (severe morning nausea without vomiting). All six of these patients were totally relieved within twenty-four hours by 50 mg. Histadyl or Benadryl morning and night and after a week were able to reduce the dosage to 50 mg. at bedtime for another week and then were told to take it only as their symptoms indicated. Five were able to discontinue the drug entirely and the sixth patient found the 50 mg. at bedtime necessary for relief.

Of this entire series, nine were gravida iii, all having had nausea and vomiting with previous pregnancies; nine were gravida ii, six of whom had had nausea with their previous pregnancy and two of whom had not. Ten were primigravidas and one was a quintigravida who had had nausea and vomiting with her last two pregnancies. Ages ranged from 19 to 37 years. With the exception of the one who aborted, all are still pregnant and progressing normally, most of them near term.

### **Nausea Induced by Diethylstilbestrol or by Hexestrol Relieved by Antihistaminic Compounds**

Since it had been shown that the nausea and vomiting caused by the synthetic estrogens, especially diethylstilbestrol, are also an allergy,<sup>2</sup> it was believed that the antihistaminic compounds should here also prevent nausea and vomiting by acting as a histamine antagonist, the mode of action being most likely that of showing a greater affinity for histamine than does the cell receptor mechanism.

Eleven patients, known to have severe vomiting after the ingestion or injection of ordinary doses of diethylstilbestrol and ten patients known to be allergic to hexestrol were given antihistaminic compounds with each dose of estrogenic drug and in each case a full therapeutic dose of the estrogen was tolerated with no side effects.

One patient, a nullipara, aged 29 years, who has been under my observation for several years because of severe metrorrhagia is of particular interest. This woman is very allergic to progesterone, developing large bullous hives following its administration. She has a plus 4 skin reaction to intradermally injected natural corpus luteum extractions. Both diethylstilbestrol and hexestrol in ordinary doses cause severe nausea and vomiting, although these two drugs in large doses, apparently by dilating the spiral arterioles of the endometrium, check her severe hemorrhaging promptly. They have been used repeatedly, during the past several years, to save frequent necessity of curettage, even though the nausea they induce is most severe.

# NAUSEA AND VOMITING INDUCED BY PREGNANCY OR BY ADMINISTRATION OF SYNTHETIC ESTROGENS; TREATMENT WITH ANTIHISTAMINIC COMPOUNDS

## A Further Study of an Additional 50 Cases

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IN PREVIOUSLY published research, the author has recorded considerable proof that the nausea and vomiting of early pregnancy are due to an allergic reaction of the patient to the secretion of her own gravid corpus luteum.<sup>1</sup> He has also shown that the nausea and vomiting which occur following the administration of diethylstilbestrol are an allergy and are similar to, if not identical with, the nausea and vomiting of pregnancy, occurring in the same individuals who have had nausea and vomiting of pregnancy and in the same degree.<sup>2</sup>

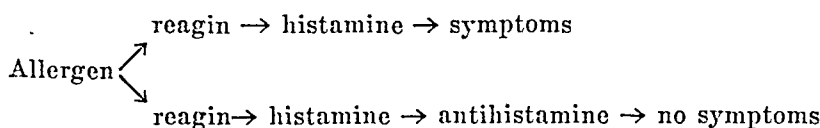


Fig. 1.—Schematic representation of mode of action of antihistaminic compounds.

Since the mechanism of allergic reactions is commonly accepted to be that of allergen + reagen → histamine release from body cells, and since one of the actions of histamine in producing allergic symptoms is to produce spasm of smooth muscle which is part of a nausea and vomiting complex, it was decided to treat a series of cases of nausea and vomiting of pregnancy with some of the antihistaminic compounds.

### Material

To date (June 19, 1948), twenty-nine cases of nausea and vomiting of pregnancy have been treated using Benadryl (beta-dimethylaminoethylbenzhydryl ether hydrochloride) in eighteen cases, and Histadyl (thenylpyramine hydrochloride) in eleven cases. Twenty-seven cases were completely relieved. One case was improved and one case was unimproved.

Of the group, three cases were classified as plus 4 (pernicious vomiting). All three of this series were tertigravidas, one aged 24 years, one 29, and one 32. One woman, about eight weeks' gestation, had been vomiting almost all ingested food and fluid for two weeks and when first seen was in a severe state of starvation, acidosis, and avitaminosis. Intravenous Benadryl in doses of 50 mg. every three hours did not alter her course any appreciable amount, although she was given, in addition, intravenous glucose and saline solution, pyridoxine hydrochloride, thiamine, and adequate sedation. She continued to vomit until she aborted five days later. The other two patients, each at about six weeks' gestation, had been nauseated eight or ten days and vomiting incessantly for two days. They stopped vomiting within twenty-four hours with 50 mg. Benadryl intravenously every four hours and were then maintained symptom free with 100 mg. orally four times a day.



Although we have not as yet been able to identify the hormone which acts as an allergen in producing the nausea and vomiting of pregnancy and/or the nausea and vomiting induced by the synthetic estrogens, I feel that this report with the facts published in previous reports is adequate proof that the symptom-complex is an allergic reaction.

With the use of antihistaminic compounds to prevent the allergic reaction, adequate, inexpensive, and prompt relief can be accorded almost all of these patients.

It might be of interest here to state that in the search for the unknown hormone which acts as an allergen several factors have been eliminated. It has been shown, in a previous publication, that progesterone is not the guilty hormone. Since that report a series of skin tests upon nauseated individuals, properly controlled, using a solution of pure relaxin, showed no correlation between the intradermal reactions and the patient's symptoms. A similar series was done using a preparation of sheep whole pituitary with like negative results. It is my opinion that the allergen will eventually be shown to be either the luteinizing hormone of the pituitary or an as yet unidentified secretion of the corpus luteum, or some metabolic by-product of one of these hormones.

### Summary

1. Twenty-nine cases of nausea and vomiting of pregnancy have been treated with antihistaminic compounds with twenty-seven cases cured, one improved, and one unimproved.

2. Eleven patients with various diagnoses, unable to take diethylstilbestrol because of nausea and vomiting induced by the drug, were given antihistaminic compounds in addition and all could tolerate the full therapeutic dose of the estrogen with no nausea or vomiting.

3. Ten patients unable to take hexestrol because of nausea and vomiting were able to take the full dose without nausea when antihistaminic drugs were added.

### Conclusions

1. The nausea and vomiting of pregnancy are allergic reactions to an unidentified hormone, probably from the gravid corpus luteum.

2. The nausea and vomiting induced by diethylstilbestrol and hexestrol are allergic reactions.

3. Antihistaminic compounds such as Benadryl or Histadyl can completely cure or prevent the nausea and vomiting induced by pregnancy or by the synthetic estrogens.

I wish to express my appreciation for generous quantities of Benadryl capsules and injectable Benadryl supplied by Parke, Davis & Co., Detroit, and Histadyl capsules supplied by Eli Lilly & Co., Indianapolis.

I wish also to thank Dr. Frederick L. Hisaw, Harvard University, for a quantity of relaxin prepared for intradermal tests. The extraction of sheep whole pituitary gland, for which I am most grateful, was furnished through the courtesy of Dr. A. A. Hellbaum, University of Oklahoma School of Medicine, and Dr. W. H. McShan, University of Wisconsin.

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Upon the last hospital admission this patient was bleeding severely. Ten mg. diethylstilbestrol were given parenterally and repeated in three hours. With the first dose, 100 mg. Benadryl were given orally and repeated at four-hour intervals. Menstruation checked markedly within a few hours and the patient was then given 18 mg. hexestrol and 300 mg. Benadryl daily (orally) for the following three days by which time bleeding had ceased. During the entire time from admission to cessation of flow the patient experienced absolutely no nausea or vomiting, much to her surprise, for she was not advised of any change in medication from that given during previous hemorrhagic periods.

Seven days before her next menstruation was due this patient was given 10 mg. progesterone in oil and 150 mg. Benadryl daily for five days. Two days later she had a normal type menstruation but had no hives for the first time in many trials endeavoring to control her hemorrhages with progesterone.

Six other patients in this series, with the menopausal syndrome, all multiparas, varying in age from 42 to 49 years, all having experienced severe nausea and vomiting with pregnancies and all having had previous nausea from diethylstilbestrol, were given 1 mg. diethylstilbestrol and 150 mg. antihistaminic compound (three cases treated with Benadryl and three with Histadyl) daily. Each patient was relieved of her varied menopausal symptoms and none of the six had any nausea from the estrogen.

Four other patients, aged 17 to 19 years, each a virgin with severe dysmenorrhea, were given 2 mg. stilbestrol and 150 mg. Benadryl daily to suppress ovulation and thus obtain a painless anovulatory menstruation. This had been tried previously but the nausea from the estrogenic drug was so intense it had to be withdrawn. With the addition of the antihistaminic there was no nausea experienced and each patient was given a painless withdrawal-type bleeding for three consecutive months while this treatment was being employed.

### Patients Allergic to Hexestrol

Another series of ten patients, who had been previously unable to take hexestrol because of nausea gave the following results:

One woman, aged 26 years, had had severe nausea with her one pregnancy seven years before. She was given 6 mg. hexestrol daily for secondary amenorrhea but was severely nauseated by it. She volunteered to take hexestrol with Histadyl experimentally to see if it would prevent the nausea. She was given 200 mg. Histadyl daily and was able to take as much as 18 mg. hexestrol daily without any nausea. After this experimental dosage, the dose was reduced to 3 mg. twice daily which she was able to take without any side effects as long as she continued 50 mg. Histadyl twice daily.

Five nulliparas, aged 19 to 24 years, who had previously been unable to take hexestrol for treatment of their dysmenorrhea, were all able to tolerate 18 mg. daily without nausea as long as they were given 150 to 200 mg. antihistaminic compound (three cases treated with Histadyl and three with Benadryl).

Four women, ages 45 to 49 years, all with previous nausea and vomiting from pregnancy and from hexestrol, were able to tolerate 3 mg. of this drug daily, which was adequate for relief from their menopausal symptoms, as long as they were given 50 mg. of either Histadyl or Benadryl with the hexestrol.

### Comment

Results using Benadryl or Histadyl were equally good, several patients being given both drugs at different times. A few patients complained slightly more of drowsiness or dizziness from Benadryl when it was first started but within two or three days they developed a tolerance to it. To prevent any side effects from the antihistaminics, I now start the patient with 50 mg. of the drug at bedtime, then have her increase the dose by 50 mg. each day until her symptoms are relieved. In this way the dosage is kept to a minimum and the side-effects are almost totally prevented.

## THE EFFECT OF DIETHYLSTILBESTROL IN THE PROLONGATION OF PREGNANCY

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IT HAS been observed<sup>1, 2</sup> that patients treated with stilbestrol for low estrogen effect alone usually went beyond term if stilbestrol was not stopped at least three weeks before the expected date. It was thought that this observation might be checked by other investigators, and the following observations are presented.

### Procedure

Since stilbestrol is now being used for threatened and habitual abortion, premature labor, and some other accidents of pregnancy,<sup>3, 4, 5</sup> thirty-five consecutive pregnant patients, among whom were nineteen threatened abortion cases and three habitual abortion cases, were given large and unphysiologic doses of "des" stilbestrol<sup>6</sup> from the first time they were seen, all during pregnancy and during labor. This was done in order to note whether the administration of stilbestrol would prolong pregnancy. It has been suggested that stilbestrol may cause the fetus in missed abortions to be retained. Two cases diagnosed as threatened abortions turned out to be missed abortions while stilbestrol was being given.

Table I gives the total number of milligrams, the number of days that stilbestrol was taken, the average daily dose, amount taken within twenty-four hours, up to and during labor, and the calculated days of pregnancy when the patient delivered.

### Summary

Thirty-five patients were given varying amounts of stilbestrol during pregnancy. The average age of these patients was 26 years, the youngest 13 and the oldest was 39.

These patients had an average of 33,320.5 mg. total dose and a daily average of 244 mg.

These patients were taking an average of 499 mg. of stilbestrol every twenty-four hours at the time of the onset of labor.

They delivered on an average on the two hundred sixty-eighth day of pregnancy, so estrogenic withdrawal at term may not be an important factor in the cause of labor. The fetuses in missed abortions were not retained, but appeared to be expelled when stilbestrol was given.

### Conclusions

It might fairly be concluded that stilbestrol, even in large and unphysiologic doses, did not prolong pregnancy in this series nor in missed abortion cases.

\*"des" diethylstilbestrol, Grant Chemical Company.

## CONTROL OF STILBESTROL VOMITING

GEORGE D. PATTON, M.D., M.S., PITTSBURGH, PA.

USE of diethylstilbestrol has been hampered by the side effect of nausea and vomiting. Other estrogenic drugs are satisfactory in treatment of the menopause, but in therapy of the functional ovarian disorders in younger women stilbestrol (as it is commonly called) remains valuable. It is economical in the large doses required and apparently more beneficial than some of the other drugs.

The author has had excellent results in treating menorrhagia, pelvic pain, and cystic ovaries with 5 mg. doses of stilbestrol. A survey of 107 such cases was published in 1945. A second series of 86 cases was published recently.<sup>5</sup> In the first series,<sup>1</sup> 50 per cent had some nausea and 9.3 per cent had to stop the drug because of vomiting.

Due to the similarity of this nausea and vomiting to that seen in pregnancy, it was decided to use the drug which has been so successful in treating the vomiting of pregnancy.<sup>2, 3, 4</sup> A single dose of 50 to 100 mg. of pyridoxine was given intravenously to all patients who complained of severe nausea or of vomiting after starting the twenty-day oral course of 5 mg. stilbestrol daily. Twenty of the 86 patients requested pyridoxine. This is higher than the 9.3 per cent of the control series who could not take the drug, but some of these twenty patients could have continued to take the drug despite their discomfort, had pyridoxine been withheld. Three, or 3.5 per cent, of the 86 continued to vomit after the pyridoxine when they resumed taking the stilbestrol. This compares with the 9.3 per cent of the control series who discontinued stilbestrol because of vomiting.

As a second control group, 18 pregnant women to whom vomiting was quite troublesome were given 50 to 100 mg. pyridoxine intravenously. Fourteen obtained relief and four were unrelieved. This is very similar to the treatment of the stilbestrol induced vomiting cases described above where seventeen were relieved and three were not.

In summary it appears that the use of 100 mg. pyridoxine intravenously will reduce by two-thirds the number of patients who are unable to take stilbestrol because of vomiting.

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TABLE I—CONT'D

NAME	TOTAL MG.	NO. DAYS TAKEN	AVERAGE DAILY DOSE	AMOUNT TAKEN IN THE 24 HOURS BEFORE AND DURING LABOR	DAY OF PREGNANCY DELIVERED
R. B. D. W-26	46,400	228	201.23	50	270
J. B. B. W-31	22,225	136	163	700	266
E. M. C. W-24	11,150	201	55.47	400	298
E. W. G. W-26	30,050	138	217.75	150	277
F. D. W-24	12,400	190	65.26	100	725

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TABLE I. SUMMARY OF 35 PREGNANT WOMEN RECEIVING "DES" STILBESTROL

NAME	TOTAL MG.	NO. DAYS TAKEN	AVERAGE DAILY DOSE	AMOUNT TAKEN IN THE 24 HOURS BEFORE AND DURING LABOR	DAY OF PREGNANCY DELIVERED
G. W. H. W-19	66,565	155	429.45	500	240
E. B. W-24	7,300	18	405.05	500	271
V. W. W-29	33,000	68	485.29	600	289
C. R. N. W-24	30,525	175	172.46	400	275
V. E. S. W-28	9,100	31	293.5	300	266
L. N. P. W-33	14,026	216	64.96	200	254
R. W. D. W-36	2,750	58	36.36	375	302
S. E. W. W-26	25,350	78	325	275	292
R. R. R. W-39	28,200	201	140.30	125	278
A. W. W-28	14,650	168	87.34	250	245
L. P. W-29	22,400	150	149.33	600	270
C. A. R. W-25	11,300	52	213.46	300	248
M. W. C-30	112,925	134	824.79	100	280
J. J. A. W-25	71,385	249	206.02	400	292
N. G. F. W-34	120,730	185	652.34	1500	223
L. M. L. W-31	25,350	260	97.5	300	299
E. M. L. W-26	22,475	85	264.4	200	263
F. J. F. W-24	6,500	70	92.85	200	257
D. A. C. W-18	5,650	143	38.81	25	207
H. M. H. W-35	84,807	213	298.15	2000	256
E. E. C. W-13	27,027	82	329.57	875	280
E. N. H. W-34	69,025	182	379.20	1000	292
A. E. E. W-26	50,825	208	244.93	100	281
J. E. P. W-24	30,505.5	104	293.32	25	268
J. P. W-25	9,650	193	50	50	302
L. M. S. W-25	33,464	874	87.14	25	312
M. E. T. W-22	10,500	58	181.03	50	266
W. D. D. W-22	33,750	195	173.07	100	243
W. W. F. W-37	36,635	77	475.78	2200	278
S. E. D. W-21	42,215.75	165	255.85	750	266

# Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

## Review of New Books

### Gynecology

**The Disorders of Menstruation and Treatment** by Colombo is a faultlessly, even luxuriously presented monograph in two parts. The ovario-pituitary relationship is considered from the experimental aspect, with extensive protocols fully illustrated, dealing mainly with castrated white rats and the effect of various attempts at replacement therapy. Many illustrations on the morphology of the pituitary resulting from these experiments are given. However, the screen is too coarse, so that interpretation of these reproductions is really impossible. In a series of noncastrated rats, as little as 275 International Units of estrogen caused marked hypophyseal changes with ovarian luteinization while, in the castrate, 4,200 International Units caused only partial restoration. No effect was produced by 1 mg. of progesterone. These experiments show nothing particularly new and gave rise to no conclusions.

The second portion is purely clinical, detailing the various general conditions which can influence the menses, taking up sterility, anovular menstruation, amenorrhea, menorrhagia and metrorrhagia, etc. Estrogenic therapy is considered but Karnaky's results evidently escaped the author's attention.

R. T. FRANK.

**Surgical Techniques by the Vaginal Route** by Eric Weber is a monograph which shows that it is written by a well-trained gynecological operator who knows the value and limitations of the vaginal route from A to Z. The book covers the entire subject. The methods for relieving cystocele and prolapse are antiquated. The description of the extended vaginal hysterectomy for carcinoma is good. The illustrations, no matter from what point of view regarded, do not come up to even the lowest standards. They are not only inartistic but in the majority of cases inadequate.

R. T. FRANK.

This large monograph by Pierre Durel<sup>3</sup> deals solely with the inflammations of the cervix, from anatomical, clinical, and therapeutic aspect. In the second edition he has the collaboration of Dutheil and Autrand. The first part deals with the histology and the clinical symptoms. The great majority of the illustrations are not up to the standards required in this country. The authors are justly against prolonged attempts at cauterization if the slightest doubt as to the possibility of malignancy exists. In diagnosis, syphilis may prove a stumbling block. They discuss cervicitis due to trichomonas. Considerable space is devoted to the laboratory bacteriology and serology for gonococcus. The therapeutic situation has been entirely altered since the first edition in which sulfonamide therapy was the main standby before the advent of penicillin. Endocrine aspects of the situation are discussed although, in my opinion, these do not apply to strictly cervical

<sup>1</sup>**Los Desordenes de la Menstruacion y su Tratamiento. Base experimental de la inter-relación prehipofiso-ovárica.** By Emilio Colombo, 327 pages. Editor "El Atenco," Buenos Aires, 1949.

<sup>2</sup>**Techniques Chirurgicales Vaginales. Possibilités et Limites.** By Eric Weber, Strasbourg. Préface du Professeur A. Labhardt. 144 pages. J. B. Baillière et fils, Paris, 6e, 1948.

<sup>3</sup>**Les Métrites du Col. Etude Anatomique-Clinique Nouveaux Traitements.** By Pierre Durel, Médecin de l'Hôpital Saint-Lazare. Avec la collaboration de Lucien Dutheil, Ancien interne de l'Hôpital Saint-Lazare et Hubert Autrand, Ingénieur I.E.N. Deuxième édition Revue et Augmentée. 333 Pages. Masson et Cie, Éditeurs, Paris, 6, 1948.

## AN AID TO THE REMOVAL OF THE GELLHORN PESSARY

D. DALTON DEEDS, M.D., SAN DIEGO, CALIF.

*(From the Department of Obstetrics and Gynecology of the Rees-Stealy Clinic)*

THE Gellhorn pessary has proved to be a very useful instrument in the treatment of prolapse of the uterus, especially in cases in which operative treatment is inadvisable. However, removal of the pessary may not be accomplished with as great ease as is its insertion; in many instances its removal may be exceedingly difficult. This difficulty is due to the inability of the operator, no matter how skillful he may be, to retain a grasp upon the small end of the pessary. A simple device has proved successful in overcoming this difficulty. A small hole is bored through the ball tip at the small end of the pessary. The teeth of a tenaculum can then be inserted at each end of the hole and a firm grasp on the pessary obtained (Fig. 1). The pessary can then be removed smoothly and easily. The tenaculum also serves as an aid in guiding the pessary during removal. The hole can be drilled in any standard Gellhorn pessary whether it be made of hard rubber or of the newer plastic materials. The openings should be smoothed to prevent irritation to the vaginal mucosa. Cleaning is easily accomplished since the hole extends through the pessary from one side to the other.

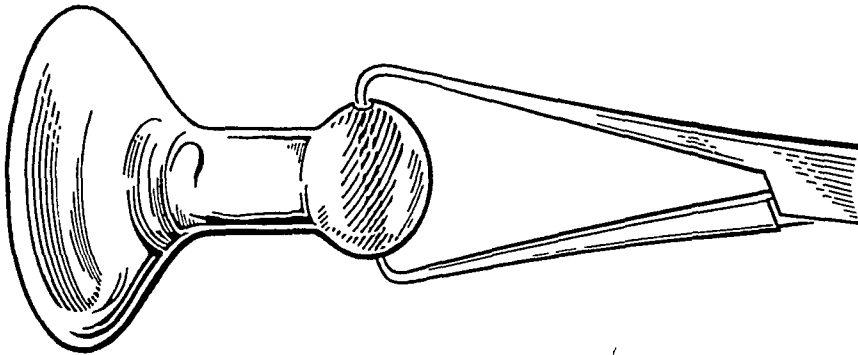


Fig. 1.—Gellhorn pessary grasped by teeth of tenaculum through hole in small end.



his treatment of heart lesions, preferring delivery from below. The chapter on cesarean section strongly emphasizes the reasons for the low incidence of cesarean section in this Georgia clinic.

This personal exposition on obstetric practice is directed toward those physicians and obstetricians who do the bulk of obstetrics in the United States. Torpin offers for them techniques which, for most conditions, can be used in the home. In this book they will find much valuable and practical information.

PHILIP F. WILLIAMS.

The proceedings of the Conference of the Committee on Human Reproduction of the National Research Council, held in New York City in January, 1948, on *The Normal and Pathological Physiology of Pregnancy*,<sup>6</sup> appear in bound form after earlier journal publication. This monograph is the sixth in a series on problems of reproduction. One conference session dealt with the subject of nutrition in pregnancy, in which Warkany discussed his recent experimental production of deformities. Darby and his co-workers demonstrated how the nutritional status during pregnancy could be assayed by biochemical methods, while Burke and Dieckmann discussed their clinical studies in the Lying-in Hospitals of Boston and Chicago, with observations and results somewhat dissimilar.

Four papers were devoted to the physiology of the toxemias of pregnancy. Page brought up to date recent research on placental dysfunction as an etiological factor. Munnell reviewed the subject of liver function in pregnancy, both normal and abnormal, while Kellogg, and Cosgrove and Chesley described certain findings in the toxemias, Kellogg from the standpoint of hemorrhagic lesions, and the latter authors more as to the clinical management.

Reynolds and his associates, in their paper on patterns of uterine contractility, give the results obtained by use of a multichannel tokodynamometer. With this method they have analyzed contractions in various types of inertia, regional retraction rings, non-dilatation of the cervix, and false and normal labor. Their study shows reasons for various types of alterations in labor mechanisms, with suggestions as to how such alterations might be treated. Peters and his co-workers suggest the determination of serum iodine as a more appropriate measurement of infertility, habitual miscarriages, or the toxemias of pregnancy. This paper is interestingly correlated by the study of Delfs and Jones on endocrine patterns in abortion. Venning discusses the mode of excretion of hormone metabolites in normal pregnancy, and Dobriner and his associates discuss the excretion of ketosteroids in normal and abnormal pregnancies.

These are outstanding contributions on the physiology of pregnancy and represent the latest word regarding intensive investigation at present being pursued in many laboratories and clinics. Only slightly less important than the material presented in the papers are the excellent discussions by other investigators following each paper.

This monograph deserves reading and study by all who are interested in the problems of reproduction for although the material is on a high scientific level there is much of practical significance in this text.

PHILIP F. WILLIAMS.

This book, *Maternity in Great Britain*,<sup>7</sup> presents the results of an inquiry into pregnancy and childbirth made in England in 1946, the basic material being 14,000 women who gave birth to a child in a certain specified week of that year. The inquiry was under the sponsorship of a joint committee of the Royal College of Obstetricians and Gynaecologists and the Population Investigation Committee.

Briefly, the investigation has attempted to answer the following questions: What services are available to women bearing children? How far are they used and what are

<sup>6</sup>*The Normal and Pathological Physiology of Pregnancy, Proceedings of the Conference of the Committee on Human Reproduction of the National Research Council, on Behalf of the National Committee on Maternal Health, Held in New York City, January, 1948. 176 pages with many illustrations and tables. The Williams & Wilkins Company, Baltimore, 1948.*

<sup>7</sup>*Maternity in Great Britain, A Survey of Social and Economic Aspects of Pregnancy and Childbirth Undertaken by a Joint Committee of the Royal College of Obstetricians and Gynaecologists and the Population Investigation Committee. 220 pages and 2 appendices. Geoffrey Cumberlege, Oxford University Press, London, New York, Toronto, 1948.*

situations. Chapters are devoted to general medical, to chemical and thermal cauterization, high frequency currents, diathermia, coagulation, and even hysterectomy in certain instances. The concluding chapter deals with metritis and prostitution particularly as it applies to the transmission of gonorrhea. The therapy of cervical conditions has been so much affected by our improvements in therapy that much simplification of this type of monograph may be expected in the future. It is a pity that the cancer situation has not been considered more fully in the monograph.

R. T. FRANK.

Another monograph by Usandizaga,<sup>4</sup> which appeared in 1946, has come into our hands. It is a second edition, the first one having appeared in 1941, forming a part of Practical Medical Manuals issued by the same publishers, a long list of which has appeared in the past. There are excellent descriptions and microscopic illustrations of erosion, its healing, and epithelial metaplasia. There are good colored macroscopic illustrations of the conditions of the cervix, their etiology and diagnosis. Especially diagnoses excluding cancer are taken up. Local therapy including cautery, coagulation, and operation are described; the sulfonamide drugs are discussed. Evidently penicillin and exfoliative cytology were not ready to be incorporated. This is an excellent, well-illustrated monograph which will have to be brought up to date soon again.

R. T. FRANK.

## Obstetrics

This *Treatise on Obstetric Labor*,<sup>5</sup> by Richard Torpin, may be regarded as expressing his personal opinions to a large degree and details the clinical obstetric practice in the hospital of the University of Georgia. The author's attitude regarding surgical obstetrical procedures is markedly conservative. He has found that employment of fluids, dextrose, transfusions, oxygen, sedation, and rest are far more favorable for the mother and fetus in many emergencies than immediate, however skillful, surgery. On his service version and extraction, except for transverse presentation, Dührssen's incisions of the cervix, and use of dilating bags have become obsolete, while postpartum packing of the fundus is necessary in approximately 1 per cent of deliveries. The ability of the uterus to expel its contents may be determined in labor by a few simple clinical tests as to the interval, length, and height of contractions, so that abnormalities, other than disproportion, may be quickly recognized and properly treated.

He has divided the material into forty-one chapters and appends a considerable list of pertinent case histories. The erythroblastosis and Rh-factor sections have been contributed by Edith L. Potter and Philip Levine. For amnesia-analgesia he prefers the intravenous use of pentobarbital sodium and scopolamine, with local anesthesia of the perineum by 1 per cent procaine solution for episiotomy.

He offers an interesting solution for rural obstetrics in suggesting and describing a delivery-room setup as a part of a rural physician's office or county health center. The patient, after such office delivery, is sent home within a few hours or the next day to convalesce in her home.

Torpin's service has seen a case of eclampsia on an average of every eighteen days over a period of ten years. The treatment of the eclamptic patient consists in the use of intravenous magnesium sulphate, the control of convulsions by pentobarbital sodium, adequate nourishment and attention to the water balance, oxygen, and, when the condition improves or becomes satisfactory, induction by rupture of the fetal membranes. He reserves cesarean section for the complete type of placenta previa and stresses the need for blood bank centers in even the smallest population centers. Torpin is conservative in

<sup>4</sup>Cervicitis. By Dr. Manuel Usandizaga, Catedrático de Obstetricia y Ginecología, Jefe de Servicio de la Casa de Salud Valdecilla. Segunda Edición. 133 pages. Manuales de Medicina Práctica. Salvat Editores, S. A., Barcelona-Buenos Aires, 1946.

<sup>5</sup>A *Treatise on Obstetric Labor*. By Richard Torpin, M.D., Professor and Chairman of the Department of Obstetrics and Gynecology, University of Georgia School of Medicine, Augusta, Georgia, 573 pages with 184 illustrations. Augusta Obstetrical & Gynecological Book Co., Augusta, Ga., 1948.

Volume I deals with normal situations. In view of the fact that 3 out of 1,000 women die in childbirth in Germany (3,500 in a year) and 5 per cent of children do so before or immediately after birth (75,000 yearly) he wants every practicing physician who does obstetrics to have at least four months of practical experience in an adequate maternity hospital. Practical advice is featured throughout.

The gross pelvic anatomy, the menstrual cycle, impregnation, early embryology, fetus, placenta, maternal pregnancy changes are adequately presented by Brickenbach. The illustrations are numerous, many in color, mostly schematic. A very elaborate exposition of the changes in the uterine muscle during pregnancy is presented, as well as other alterations in the maternal organism including such divergent subjects as chemistry of the blood, joint changes, and alterations in the adenohypophysis.

External and internal examination, pregnancy test, mensuration, determination of term, all profusely illustrated, are described. Under the subject of labor, the pelvis, the birth canal, the passenger, the forces at work, etc., are dealt with; finally, the course of a normal labor with digression in various directions. The conduct of labor by a midwife is next described, vaginal examination alone is indicated, median episiotomy recommended. The various normal positions are given in great detail, followed by multiple pregnancies. Nordmeyer is the author of the chapters on the puerperium and lactation and the physiology of the neonatus. This volume alone boasts of 539 illustrations.

Volume II contains the pathology, divided into four sections—disturbances of pregnancy, disturbances of labor, pathology of the puerperium, and the sick newborn. I have selected a few high spots for consideration. In threatened abortion the treatment with large doses of stilbestrol is not yet recommended. Emptying of the uterus is done in two stages by means of dilatation with laminaria for eight to twelve hours, next quinine and oxytocin, followed by curettage. Descriptions of extrauterine pregnancy, hydatid and chorionepithelioma with many colored illustrations are adequate. Much space is devoted to diseases of the pregnant woman. In eclampsia prophylaxis, Stroganoff treatment, venesection, and finally cesarean section are counseled. Malpositions, spontaneous and those due to pelvic or to fetal malformations or to malformations of uterus and vagina are described. In hospital practice, cesarean section is recommended for the uninfected patient with placenta previa. Penicillin apparently is just becoming available and is mentioned in the treatment of gonorrhea and as a possible means of combating puerperal sepsis.

Volume III corresponds to the sixth edition of Martius' book on obstetrical operations which first appeared in 1934. He not only emphasizes the dangers of the high forceps but believes that modern obstetrics would be improved by complete abandonment of this procedure. Classical cesarean has been abandoned universally. He describes the various suprasymphysial techniques. The book differs little from the earlier editions which have been received with much favor.

The three volumes form a comprehensive and adequate presentation of the subject. They are somewhat large and voluminous for the average student and even for the general practitioner but valuable for the specialist.

R. T. FRANK.

The Third American Congress on Obstetrics and Gynecology was held in St. Louis in September, 1947. The previous meeting had taken place in 1942. A large number of organizations are members of this Congress. The Proceedings<sup>9</sup> cover everything minutely from invocation to the final manikin obstetric demonstration and the list of motion pictures which were shown, covering a total of 412 pages.

The contents covers the most diverse material, such as the advantages of the rooming-in unit in obstetric hospital; symptoms of sterility from every aspect; round-table dis-

<sup>9</sup>Transactions of the Third American Congress on Obstetrics and Gynecology. Municipal Auditorium, St. Louis, Missouri, September 8 to 12, 1947. Sponsored by the American Committee on Maternal Welfare, Inc. Edited by George W. Kosmak, M.D., and Robert N. Rutherford, M.D. 412 pages. Published by the Western Journal of Surgery Publishing Company. Portland, Oregon, 1948.

the factors affecting their use? Do they help women to regard childbirth as a normal process? How far do they prevent premature birth and infant death and promote the health of mothers and infants? Finally, what do parents spend on pregnancy and childbirth?

The method used in the inquiry seems to have been sufficiently broad to complete the aims and one can feel that the sample was adequate as to regions, frequency of births, housing, social classes (economic) and in relation to frequency of stillbirths and neonatal deaths. The subject matter of the text develops all of the general problems of maternity, antenatal care, care during confinement, relief of pain, and an extremely interesting chapter on the costs of childbearing.

In 1936, the English well-to-do apparently spent an average of \$228 for the first baby, while manual workers' wives spent \$144. Less money was spent for subsequent births, and poorer mothers economized progressively as their families grew in size. There was, of course, a marked difference among women who received care under municipal schemes. A section discusses the provisions of the National Health Service Act for free confinement care which has not removed many of the economic obstacles to childbearing in Great Britain.

Such special aspects of the maternity problem as prematurity are brought out. The conclusion is drawn that a reduction in prematurity should be expected from the improvement in the quality of the antenatal service rendered in Great Britain. As to the topic, "Infant Feeding," it is shown that 43 per cent of the inquiry mothers are wholly bottle feeding their babies at the end of the eighth week, and again the editors of the report feel that antenatal supervision stands out as a more important factor in the maintenance of lactation than any other factor. As to women in industry, it was found that most of the primigravidas employed in gainful occupations during pregnancy terminated their employment in mid-pregnancy and only a few, a small proportion of them, intended, at a date two months after the delivery, to resume such occupation. Home nursing received attention in the report. Illegitimately pregnant women suffered with respect to antenatal care; as to confinement care, it was about equal with others. In regard to economic circumstances these women were at a great disadvantage as compared to married women. Many became destitute and the assistance available to them in Great Britain was considered most inadequate.

The concluding chapter has many sound recommendations for the improvement of the faults brought out in the inquiry. It will be interesting to see a repetition of such an inquiry after the National Medical Service Act has been in operation for a few years.

For those who are interested in the social and economic aspects of pregnancy and childbearing, and all physicians should be interested, the book offers a great deal of value.

PHILIP F. WILLIAMS.

A three-volume **Obstetrics—Physiology, Pathology, Operations** by Martius, assisted by Bickenbach, Nordmeyer, and the artist, Käthe Droysen, is the first important German contribution submitted to us since World War II. The publisher is the old firm of Georg Thieme, now in Stuttgart. I do not know why the ages and birthplaces of the authors are given—perhaps a military regulation; also the number of copies printed, 4,500. The object is to present a simple, noncontroversial exposition for students and physicians. The illustrations, in the main, are new.

**Lehrbuch der Geburtshilfe.** von Prof. Dr. Med. Heinrich Martius, Direktor der Universitäts-Frauenklinik Göttingen. Unter Mitarbeit von Professor Dr. Med. Werner Bickenbach; Professor Dr. Med. Kurt Nordmeyer; Käthe Droysen als Zeichnerin. Erster Teil: Physiologie, Unveränderter Neudruck. Mit 539, Zum Teil Farbigen Abbildungen. 568 pages. Zweiter Teil: Pathologie, Unveränderter Neudruck, Mit 486, Zum Teil Farbigen Abbildungen. 605 pages. Georg Thieme Stuttgart, 1948.

**Die Geburtshilflichen Operationen.** Ihre Ausführung und Anwendung. Ein Lehrbuch für Studierende und Gebrauchsbook für Ärzte. von Prof. Dr. Med. Heinrich Martius, Direktor der Universitäts-Frauenklinik Göttingen. Sechste Auflage. Mit 281 Abbildungen. 287 pages. Georg Thieme, Stuttgart. 1948.

This comprehensive study of the **Control of Pain in Childbirth**,<sup>11</sup> by Lull and Hingson, appears in a third edition. The discussion of the drugs which may be used for this purpose includes the characteristics of each agent, an exposition of the pharmacologic action, a re-evaluation of the toxic effect of the drug, the technique of its use, the advantages, disadvantages and dangers, as well as the technique for the administration of each agent. The possible fetal complications resulting from the use of the various agents have also been described, and the drugs are evaluated from the standpoint of fetal salvage.

The book has been brought thoroughly up to date. Among the prominent revisions in this third edition is the considerably rewritten chapter on the anatomic considerations in regional nerve block, with special reference to caudal anesthesia. Another section which is new is devoted to the early care of the newborn infant, particularly in reference to the agent which may have been used in its delivery. There has also been added a discussion of the continuous caudal anesthesia study at Memphis, Tenn. The material there includes more than 5,000 continuous caudal, 2,500 saddle-block spinal and continuous spinal, and 800 births with general anesthesia. The statistical analysis of this group is compared with the results in the Philadelphia study. The figures and results are impressive and fully support the conclusions formed by the original study in the Marine Hospital on Staten Island.

Among other new material particularly is noted inclusion of the report from the Chicago Lying-in Hospital of spinal (saddle-block) anesthesia in obstetrics, with a full description of its use in 719 cases and the results as to pain relief, interference with labor mechanism, and the fetal respiratory processes. The present wide use of Demerol and scopolamine is well analyzed.

The book is almost encyclopedic in character, and although caudal anesthesia receives the largest degree of attention, every drug has been evaluated and there are many chapters of general interest, such as the one on psychology in pregnancy, in which the authors discuss and give their opinion of Reed's thesis on childbirth without fear, management of the puerperium, pain relief in home obstetrics, and the question of pain relief when maternal complications are present. The book is profusely illustrated and may be recommended as a practical working guide to all who are interested in pain relief in labor.

PHILIP F. WILLIAMS.

Many years of clinical experience and teaching have eminently fitted Miss Alice M. Hunt to write this book, **Anesthesia**,<sup>12</sup> which is primarily intended for the nursing profession. A reading of this volume should give nurses a clear and practical concept of the subject. After a brief, but interesting, historical review she stresses the dangers of the various agents used, and discusses the disadvantages as well as the benefits of premedication. She concludes that a proper choice of such drugs depends upon good judgment in relationship to the situation of each individual patient. Equally, she brings out the need for close care and watchfulness until the patient's return to the conscious state is completed.

Various agents, liquid, gaseous, Avertin, and those used intravenously or in local or regional anesthesia, are described as to their choice and action. Miss Hunt devotes considerable space to obstetric analgesia for the stage of dilatation, and analgesia and anesthesia for the stage of expulsion, both from the standpoint of relieving pain and from the standpoint of operative obstetrics. She feels it is unlikely that caudal anesthesia-analgesia for obstetrics will become routine. She suggests a trial of the psychological dissipation of the fear of labor as proposed by Reed. This fear, she states, creates increased tension in the opposing muscles of the corpus and of the cervix in labor, and the counteraction

<sup>11</sup>**Control of Pain in Childbirth.** By Clifford B. Lull, M.D., F.A.C.S., F.I.C.S., Director, Division of Obstetrics and Gynecology, Philadelphia Lying-In Unit, Pennsylvania Hospital, and Robert A. Hingson, M.D., F.I.C.S., F.A.C.A., F.I.C.A. Third Edition. 508 pages with 171 illustrations and 10 color plates. J. B. Lippincott Company, Philadelphia, London, Montreal, 1948.

<sup>12</sup>**Anesthesia: Principles and Practice, a Presentation for the Nursing Profession.** By Alice M. Hunt. 137 pages with 7 illustrations. G. P. Putnam's Sons, New York, 1949.

cussions (for example, asphyxia of newborn, prolonged labor, uterine myomas, early controlled ambulation, etiology of abortion, and Rh studies in 28,500 pregnant women). For the general meetings, such major subjects as follow were discussed in multiple presentations—analgesia and anesthesia; emotional aspects of pregnancy; cancer of cervix; cesarean section. The volume contains a fund of information and a valuable exchange of opinion in a free and unhampered forum.

R. T. FRANK.

The text of *Obstetric Analgesia and Anesthesia*,<sup>10</sup> by Franklin F. Snyder, is divided into two sections, respiratory injuries of the child and the treatment of pain during labor. It discusses the present status of pain-relieving drugs from both an experimental standpoint and clinical use in obstetrics. The author states that obstetric analgesia is today the most widely discussed and the most controversial problem in obstetrics, and that the wide use of pain relief in labor has introduced a new factor, anesthetic drugs, into our consideration of the outcome of labor.

Dr. Snyder states that fetal respiratory injury is pre-eminent as a cause of death associated with birth. He points out the obvious fact that we must now add a measurement of this new pharmacologic factor influencing the fetus to our former regard only for the mechanism and the fetal environment. At present, the author suggests, the introduction of new methods of analysis permits the comparison of one agent with another in terms of the amount of respiratory depression in the fetus, and the degree of impairment produced in the labor mechanism. The application of such methods has facilitated the clinical trial of the drugs currently used in obstetric analgesia-anesthesia. They permit a determination of the margin of safety, not only for the mother but especially for the child, when we attempt to evaluate an agent in terms of potency of relief of pain, effect upon the fetus, and effect upon the labor mechanism.

In the discussion on respiratory injuries of the child, the author expands his ideas on the pharmacologic factors in labor, the mechanism of intrauterine respiration and the incidence of respiratory injuries before birth such as pneumonia, atelectasis, and asphyxia. He describes, in Chapter Seven, the laboratory methods by which the various agents may be assayed in regard to their effects upon both mother and fetus. By this assay the pharmacologic factor may be measured quantitatively in terms of depression of fetal respiration and impairment of the uterine expulsive mechanism.

In the section on treatment of pain during labor, the different agents are evaluated singly as to their potency, risk, and effect. The author discusses morphine, scopolamine, and the barbiturates in this regard, and proceeds to an evaluation of the rectal use of ether, alone or in combination of other agents and with certain synergistic drugs, and the rectal use of Avertin is discussed. He has analyzed the use and results of inhalation of ether and of chloroform and the narcotic gases, nitrous oxide, ethylene, and cyclopropane. The concluding chapter discusses the use of regional anesthesia in terms of physiology, technique, and the effects upon the mechanism of labor and on the fetus. Thus, we find caudal anesthesia, spinal, the different types of nerve block and local infiltration methods analyzed as to their risks, disadvantages, advantages, and effects.

The author, who has made outstanding contributions to the subject and study of fetal respiration, has ably compared studies in physiology of the fetus with the clinical results of the drugs now employed for relief of pain in labor. He has analyzed at length the pharmacologic factor introduced through the widespread efforts to promote analgesia. He has thoroughly reviewed the clinical reports available and has demonstrated how the effects of various agents can be assayed. Dr. Snyder presented a very fine study of a most important problem in the practice of obstetrics.

PHILIP F. WILLIAMS.

<sup>10</sup>*Obstetric Analgesia and Anesthesia, Their Effects Upon Labor and the Child.* By Franklin F. Snyder, M.D., Associate Professor of Obstetrics and Associate Professor of Anatomy, Harvard Medical School. 385 pages with 114 illustrations. W. B. Saunders Company, Philadelphia and London, 1949.

parturition. She devotes some pages to an exposition of Reed's principles and then, in a well-illustrated text, describes and shows the calisthenic exercises which it is felt will help enable a woman to achieve a painless labor and a spontaneous delivery.

The material is presented for the benefit of obstetricians and physiotherapists who may wish to teach these methods to pregnant women, either singly in private practice, or in small ward classes in a hospital service. The method is so well illustrated that teachers should have no difficulty in explaining the exercises to pregnant women. There are also exercises which should be of help in the puerperium and a description of breast massage by the physiotherapist which it is felt may promote lactation and make breast feeding easier.

This book should be of value to those who wish to teach the physical phases of Reed's method.

PHILIP F. WILLIAMS.

A book published in 1942 by Usandizaga on the **Pathology of the Pelvic Articulations During Pregnancy**<sup>10</sup> has arrived belatedly. It appeared simultaneously in Madrid, Barcelona, Buenos Aires. It takes up the anatomy of the joints, the alterations produced by pregnancy, including particularly the relations and consequent development of pain, particularly in the lumbosacral region.

R. T. FRANK.

The **History of Obstetrics and Gynecology in Spain**,<sup>11</sup> by Usandizaga, professor of Obstetrics and Gynecology of the Faculty of Medicine of Zaragoza, was published in Santander in 1944. There are a number of histories of Spanish medicine, for example Chinchilla, 1941; Hernández-Morejón, 1942, and García del Real which was published in 1934, but they do not consider sufficiently obstetrics and gynecology. The volume deals mainly with the early history, starting with the Romans and Saracens, the medieval and religious eras, featuring Francisco Lopez of Villalobos, who practiced somewhere between 1473 and 1542, and who had an excellent knowledge of gynecology and obstetrics, spoke of sterility due to poor semen, other sterilities due to uterine trouble, discusses abortion, mole, dystocia, menorrhagia and metrorrhagia, etc. The era of witch doctors, monsters, etc., follows. The pregnant woman and lactation; their importance in Spanish literature and church are taken up. Men were permitted to attend childbirth in about the 18th century, much later than in France. There is a very realistic series of sculptures of pregnancy with the womb in situ, now found in the medical college of Madrid, dating from the eighteenth century, ascribed to the supervision and dissections of Gimbernat. They compare very favorably with some of our most modern models. He records that the first cesarean in Spain was in 1753 and was performed for transverse position. In 1779, the first symphysiotomy was done in Spain. At that time perineal expression of the head was practiced. The history of the nineteenth century is added as an appendix. This book is most profusely illustrated with rare and uncommon pictures and also has a bibliography.

R. T. FRANK.

Pizon is the author of a monograph on **Obstetrical Radiodiagnosis** as part of the series, "L'Expansion Scientifique Française." The subject is adequately covered in brief form, including visualization of the fetus after it has attained the length of 20 cm.; the recognition of fetal death; fetal malformations; afterbirth; the determination of age by bone; the recognition of age of fetus. He describes the pelvis, radiopelvimetry as well as radiocephalometry. A special chapter is devoted to the radiology of the placenta, the recognition of extrauterine pregnancy and of uterine rupture. There are a considerable bibliog-

<sup>10</sup>**Patología Grávidica de las Articulaciones Pelvianas.** By M. Usandizaga. Primera Edición. 120 pages. Ediciones Morata, Madrid, Barcelona, Buenos Aires, 1946.

<sup>11</sup>**Historia de la Obstetricia y de la Ginecología en España.** By M. Usandizaga. Cate-drático de Obstetricia y Ginecología de la Facultad de Medicina de Zaragoza, Jefe de Servicio de la Casa de Salud Valdecilla. 361 pages. Santander, 1944.

<sup>12</sup>**Radiodiagnostic Obstétrical.** By Pierre Pizon, Ancien Assistant d'Electro-Radiologie des Hôpitaux de Paris. 161 pages. L'Expansion Scientifique Française, 1948.

is the origin of much parturient discomfort. She refers to the excellent results obtained at the New Haven Hospital and feels the method is deserving of a wide trial, at least in normal cases. The book closes with an excellent presentation on oxygen therapy to which, in a future edition, the author might well add some material on resuscitation.

The book is not only an excellent presentation for the nursing profession but offers as well an excellent and concise review of anesthesia for physicians.

PHILIP F. WILLIAMS.

This perennial and popular review of the obstetric and gynecologic literature of the world as selected by J. P. Greenhill, the 1948 Year Book,<sup>13</sup> comes to hand. There are 262 pages of abstracts on obstetrics and 322 pages of abstracts on gynecologic topics. An increasing number of references denotes an added widespread interest in the subjects of nutrition, the antibiotics in both specialties, and the influence of virus infections on the embryo. Twenty-five pages are devoted to abstracts on anesthesia-analgesia during labor. There is a recapitulation of Reed's methods. Greenhill continues to express his preference for infiltration techniques for obstetric surgery.

In the section on gynecology a very interesting discussion brings up the legal problems arising from the practice of artificial insemination, and it may well be read by those who use this method in the treatment of infertility. Quite a number of new operative procedures are described as well as a number of modifications of standard techniques. This part of the book is profusely illustrated. There are many references on the cytologic diagnosis of cancer, and 47 pages are filled with references to pelvic malignancy. The physiology of both subjects is full of new research.

As usual, Greenhill adds many personal notes in his editorial remarks. While not as sharply critical as in former years, the editor does not fail, however, to express vigorous dissent as he sees it. Once again, a list of questions is posed to test one's familiarity with the current literature.

PHILIP F. WILLIAMS.

*Safeguarding Motherhood*,<sup>14</sup> by Sol T. DeLee, is another manual for the expectant mother. Dr. DeLee has given an excellent discussion of pregnancy and parturition in language which should be easily understood by the average individual, and with enough development of the material on anatomy and physiology to satisfy the most curious. The subject of mental and physical hygiene includes a section on nutrition and the diet. The printed diets and the calorie tables should help a woman limit her weight gain during pregnancy. The minor disorders and the major complications of pregnancy are simply stated and the mechanism of labor and the use of some operative procedures are briefly described. Excellent directions are given for the puerperal hygiene and postpartum problems. Dr. DeLee discusses the return of menstruation and the various methods of birth control. The final chapter is practical advice on the normal newborn child and its care. Most of the questions that are usually asked by an expectant mother of her physician, Rh, early ambulation, rooming-in, determination of sex, calculation of date of delivery, signs of labor, suggestive symptoms of complications, are answered here. The book is well recommended as an aid in the instruction of an obstetric patient.

PHILIP F. WILLIAMS.

In this small book, *A Way to Natural Childbirth*,<sup>15</sup> Miss Heardman presents a detailed description of the methods by which the expectant woman may be trained to relax during

<sup>13</sup>The 1948 Year Book of Obstetrics and Gynecology. Edited by J. P. Greenhill, B.S., M.D., F.A.C.S., Professor of Gynecology, Cook County Graduate School of Medicine; Attending Gynecologist, Cook County Hospital; Attending Obstetrician and Gynecologist, Michael Reese Hospital. 584 pages with 110 illustrations. The Year Book Publishers, Inc., Chicago, 1949.

<sup>14</sup>Safeguarding Motherhood. By Sol T. DeLee, M.D., Clinical Instructor of Obstetrics and Gynecology, University of Illinois; Attending Obstetrician at the Chicago Maternity Center. 119 pages with 42 illustrations. J. B. Lippincott Company, Philadelphia, London, Montreal, 1949.

<sup>15</sup>A Way to Natural Childbirth, A Manual for Physiotherapists and Parents-to-Be. By Helen Heardman, Diploma Bedford Physical Training College, Chartered Physiotherapist (Teacher's Certificates). With 119 pages and 66 illustrations. The Williams & Wilkins Company, Baltimore, 1948.



Here Dr. Dunham has described the physiologic handicaps of the premature infant with detailed information as to care in the neonatal period, as well as methods of overcoming the definite nutritional handicaps. The prevention and therapy of other lesions or diseases particularly affecting the premature infant are amply described, from a preventive as well as a therapeutic aspect.

The appendixes, nine in number, are of value not only from certain statistical viewpoints but also for the detailed discussions and specifications for incubators and methods of feeding. There are many well-reproduced photographs, drawings, schematic representations of normal and pathologic sections of the systems, and of developmental sequences.

The literature is profusely quoted. The documentation is thorough and there are extensive bibliographies following each section. The manual covers the subject widely. It is a reference book of excellent value, and the practical suggestions as to treatment make the book highly recommended for everyday use.

PHILIP F. WILLIAMS.

The American Academy of Pediatrics in cooperation with the United States Public Health Service and the United States Children's Bureau has made a nationwide study of **Child Health Services and Pediatric Education**.<sup>21</sup> The book is divided into two parts. Part One brings out the high lights of the actual information gathered in relation to private practice, hospital facilities, and the services of community health agencies. The second part deals with an evaluation of pediatric education, an analysis of all of the medical schools in the United States and all of the hospitals approved for pediatric residencies. There is a tremendous amount of informative material in both divisions of the text.

The diversities and inadequacies of the medical service given to babies and children in the United States apparently depend on the availability of competent general practitioners who are in charge of three-fourths of the private care of such children. The report stresses the need for more clinical instruction in pediatrics of undergraduates and suggests financial aid in fellowships to train specialists and the promotion of graduate training for general practitioners. Indeed, the whole problem on how to make good medical care available and adequate for all children would seem to be answered by an early expansion of pediatric education in the medical school to the practicing physician.

In so far as the newborn is concerned, it is shown that births in hospitals have increased from 37 per cent of all babies in 1935 to 82 per cent in 1948. In metropolitan centers only one birth in twenty took place at home while in isolated rural counties more than 50 per cent were house confinements. Hospital delivery, in many instances, is considered deficient in respect to certain selected characteristics such as nurseries for full-term sick babies separated from well babies, the lack of a house staff to care for the newborn, the lack of an isolated formula preparation room, the lack of a practical nurse on continuous duty in the nursery, and the use of unsterilized milk for the newborn.

The report states that training of physicians in the care of the newborn is a cardinal duty of the medical school. Because of the possibility of cross infection if ward classes are permitted in nurseries and since the problem involves both the obstetric and pediatric departments, such teaching presents a difficult problem in undergraduate education. It is felt that instruction as to care of premature infants is far less effective than for normal newborns. In a large percentage of hospitals the pediatric department does not have control of the newborn service. The training of residents in the care of the newborn and premature infant is undoubtedly incomplete in many hospitals. There are twenty out of 178 hospitals approved for pediatric residents' training which provide no experience at all in the care of the newborn or premature.

The logical subsequent step to this statement of inadequacy is "What is going to be done about it?" and the institutions concerned in the report are already making recom-

<sup>21</sup>**Child Health Services and Pediatric Education.** Report of the Committee for the Study of Child Health Services, The American Academy of Pediatrics, with the cooperation of the United States Public Health Service and the United States Children's Bureau. 269 pages. The Commonwealth Fund, New York, Oxford University Press, London, 1949.

raphy and fifteen excellent plates. While this monograph contains nothing new, it is an excellent exposition of the subject, particularly for those not especially interested in minute technical details.

R. T. FRANK.

## Pediatrics

Pregnancy wastage which takes an enormous toll of life has been fully discussed in this monograph on **Fetal and Neonatal Death**,<sup>19</sup> by Edith L. Potter and Fred L. Adair. After a full description of intrauterine life from fertilization to term, the authors give in detail the correct technique of a postmortem examination of the fetus, proposed by them because of the marked difference in brain and heart lesions of adult and fetal organs. The technique suggested should result in bringing pathological changes more exactly to the attention of the obstetrician. The authors, pointing out the difficulty of determining the cause of death in many fetuses, feel that undoubtedly lethal factors are inherent in the germ plasma in many instances. The etiology and types of malformations are discussed, as well as the other causes of fetal and neonatal death, such as anoxia, birth trauma, prematurity, toxemia, and infections. Reference is made to the influence of virus infection on death and malformations of the embryo. Anoxic deaths are regarded as only those in which the primary cause of death lies outside the fetus. Obstetricians may read with benefit the section on birth trauma. Prematurity, the authors state, should not be considered a cause of death in the stillborn fetus. Unless some pathologic condition is present the fetus should be born alive. The authors feel no evidence has been presented that toxemia of pregnancy affects an infant after delivery, and they point to pneumonia as the most common infection in the newborn infant, stressing the influence of prolonged labor in which the membranes have ruptured early. Special pathology of systems is developed at some length. There is a short but excellent section on erythroblastosis. The statistics of the Chicago Lying-in Hospital and of the National Office of Vital Statistics have been brought well up to date, and the definitions and classifications in present use are stated.

The tremendous reduction in the maternal mortality rate which occurred in the United States in recent years points to the likelihood that a thorough and painstaking analysis of every fetal or neonatal death in the manner which the authors describe would do much to promote a striking increase in fetal salvage.

PHILIP F. WILLIAMS.

Dr. Ethel C. Dunham, who for many years was a consultant on prematurity for the Children's Bureau of the United States Government, has brought together a tremendous amount of material of both statistical and clinical value in this publication, **Premature Infants, a Manual for Physicians**,<sup>20</sup> issued by the Federal Security Agency. Since the loss of life following premature births accounts for one-half of infant deaths in the first month of life, the need for such an excellent presentation of the whole subject is clearly apparent.

The text, of nearly four hundred pages, is divided into two parts. The first part, which may be regarded as a source of information in regard to prematurity, deals with such general considerations as the definition of and the criteria for prematurity, the statistical material as to the incidence, and cause, and the prevention of premature birth, the death rates and the causes of death, as well as the growth and development of premature infants. This section provides an excellent background for the clinical material and suggestions for the general care of premature infants which form the second part of the book.

<sup>19</sup>**Fetal and Neonatal Death, A Survey of the Incidence, Etiology, and Anatomic Manifestations of the Conditions Producing Death of the Fetus in Utero and the Infant in the Early Days of Life.** By Edith L. Potter, M.D., Ph.D., Associate Professor in the Department of Obstetrics and Gynecology, the University of Chicago, Pathologist at the Chicago Lying-in Hospital, and Fred L. Adair, M.D., Mary Campau Ryerson Professor Emeritus, the University of Chicago. 167 pages with 38 illustrations. The University of Chicago Press, Chicago, 1949.

<sup>20</sup>**Premature Infants, a Manual for Physicians.** Children's Bureau Publication No. 325. By Ethel C. Dunham, M.D. 341 pages with 31 illustrations. Federal Security Agency, Washington, 1948.

hormones, those of growth and others such as wound, flower-forming, and leaf-growth substances (Auxins and phytohormones, both those found in nature and the synthetic not so found).

Berta Scharrer deals with hormones in insects which play an important role in reproduction, postembryonic development, and production of hereditary characters (gene hormones). Whether insects secrete real sex hormones is controversial. A growth and differentiation hormone and a juvenile (inhibiting) hormone are recognized; also a number of organs which produce the hormones.

Frank A. Brown describes the hormones found in crustaceans. None of them has been obtained in a pure state. Parasitic castration modifies both male and female characters but no sex hormone has been demonstrated as such. An eyestalk hormone, not species specific, controls the melanophore action (sinus gland); also two from within the central nervous system (lightening and darkening hormones). Retinal pigment movement is likewise ascribed to hormonal control.

Greengard has written the chapter on "Hormones of the Gastrointestinal Tract." The four from the upper intestine—secretin, pancreaticozym, cholecystokinin, and enterogastrone are best known. They have in common that no special cell group has been identified as their source, that their effect is limited to the organs of digestion, that their chemical make-up is unknown.

Roy O. Greep discusses the physiology and the chemistry of the parathyroid hormone. It is a well-rounded presentation, embracing physiology, relation to other glands, the hormone itself including preparation, effect on bone metabolism and clinical symptoms of over- and underproduction, its relation to pregnancy and lactation.

Jensen has written the chapter on the internal secretion of the pancreas. Crystalline insulin from various sources is identical and develops an effect of 24 I.U. per mg.

The next six chapters have an entirely different tone and aspect. They deal with the estrogenic, progestational, androgenic, and adrenal steroids which have been isolated, their structure determined, and many synthetically reproduced and active synthetic chemicals of similar action not occurring in nature which have been discovered. Dorfman, for example, who handles the biochemistry of the androgens, gives a list of 118 compounds. Pincus discusses assay of ovarian hormones, Pearlman the chemistry and metabolism of estrogen and those of progesterone as well. The chemistry and metabolism of the adrenal cortical hormones have been covered by R. D. H. Heard. These chapters are almost entirely theoretical chemistry with emphasis on chemical rather than biologic aspects and methods.

The chemistry of the anterior pituitary hormones has been written by Cho Hao Li and Herbert M. Evans. They recognize interstitial cell stimulating and lactogenic hormones, adrenocorticotrophic and growth hormones "isolated in pure form," the follicle-stimulating and thyrotrophic less purified. Whether their interpretation of purification should be accepted without reserve, I am not qualified to decide. These hormones certainly do not give clear-cut reactions on human beings as other pure products do.

The next chapter, that dealing with hormonal control of mammary growth (by Folley and Malpress of Reading, England), is of particular interest to me. Lured into endocrine research in 1906 by the spectacular report of Lane-Claypon and Starling on mammary growth induced by fetal, ovarian, and placental extracts, I spent an entire year of hard work only to discover that their aqueous extracts were inert and that their results were accidental and actually due to the ovarian cycle, which they had completely overlooked, mainly because they had neglected to use controls. "An Experimental Study of the Causes Which Produce the Growth of the Mammary Gland" (Arch. Int. Med. 7: 665, May, 1911). This erroneous work, which Starling never deigned to repudiate, still crops up perennially in the literature. Even today no exact clarification of the mammary cycle can be given. The estrogens, corpus luteum and adrenocortical as governed by the pituitary stimuli, produce growth but the placental influence, as described in minute detail by Halban in 1905, predominates. This classic, and in my opinion epochal paper, by the way, is not even mentioned by

mentations based on all levels. There are few connected in any way with the care of child health service, practice, administration, or education who will not find much of interest in this report.

PHILIP F. WILLIAMS.

In this psychological analysis of a child from birth to marriage, *Your Child's Mind and Body*,<sup>22</sup> Dr. Flanders Dunbar has given practical answers to the usual as well as the most infrequent emotional problems. Dr. Dunbar very effectively discusses the problems of the infant in relation to the functions of rest and nutrition. In both situations, she explains, the parent has a dual responsibility not only to understand his child, but also to help the child understand him and consequently to understand the outside world. In these respects the child's future is determined, she states, not so much by what you say but by the way you say it.

Her recital of the self-selection experiment of the diet by infants should reassure many anxious parents in regard to the food desires of their children. Dr. Dunbar describes play as an experiment, to be allowed as freely as possible without parental interference, to permit the child to acquire a sense of causes and consequences. In other words, to develop objectivity. In discussing psychopathic behavior she states that the best guard against having a problem child is coming to terms with yourself sufficiently to avoid being a problem child to yourself and to your neighbors. She discusses the relationship of marriage to the emotional situations of a child, and feels that parents insecurely united usually have insecure children.

There is an excellent chapter on the subject of training a child, obedience, punishment, and building a child's character. The author feels that the emotional patterns of six years are definitely present and accentuated at sixteen, and that "obedience" should be kept out of the child-parent relationship as far as possible. The psychologic bases of minor or major crimes are thoroughly explained. The author does not feel it is ever too late to begin training to correct such disorders.

The final chapter on the child nearing maturity deals with the problems of sex and contemplated marriage and describes for both child and parent the partial relinquishing of certain home and family ties for new personal relationships. At the end of the text, and in addition to an index, Dr. Dunbar has tabled the emotional problems as they occur between the ages of one month and seven years, so that the interested parent may follow one problem or another through the various periods of development.

This is an excellent manual for parents, and it is also a good book for the physician who is called on to guide parents through the field of child care.

PHILIP F. WILLIAMS.

## Endocrinology

**The Hormones. Physiology, Chemistry and Applications**,<sup>23</sup> edited jointly by Pincus and Thimann is a two-volume work of which Volume I now is at hand. It is an attempt to bring together "a comprehensive presentation at the research level." Experimentalism receives full emphasis; where possible, practical applications to biology and medicine are featured. Volume I contains the chemistry, the role of the hormones in other than mammals, and some aspects of animal physiology, treated by fourteen authors of whom eleven are American and one each Canadian, English, and Irish. Volume II will cover mammalian endocrinology with clinical application. Volume I deals mainly with chemical physiology. It is written by chemists and appeals mainly to the chemist though, in part, it is of interest to and understandable by the physician. Thimann in two chapters discusses plant

<sup>22</sup>*Your Child's Mind and Body, a Practical Guide for Parents.* By Flanders Dunbar, M.D. 292 pages. Random House, Inc., New York, 1949.

<sup>23</sup>*The Hormones: Physiology, Chemistry and Applications.* Edited by Gregory Pincus, Worcester Foundation for Experimental Biology, Shrewsbury, Mass., and Kenneth V. Thimann, Harvard University, Cambridge, Mass. Volume I. 886 pages. Academic Press, Inc., New York, 1948.

## Miscellaneous

This book, *Clinical Aspects and Treatment of Surgical Infections*,<sup>27</sup> by Frank Lamont Meleney, is a systematic review of the surgical infections. It is based on the author's experience of more than twenty-five years as both a clinical surgeon and a practical as well as a research investigator of the pyogenic and necrotizing organisms found in surgical infections. Chapters in the book have been contributed by former associates of the author: Lockwood, Harvey, Longacre, and Sandusky. The last two have written on surgical infections in war wounds.

The book is truly a history of the treatment of surgical infections over the period of three decades. The author describes the treatment of these bacterial invasions before the advent of sulfonamides, during the time they were first introduced, and since the availability of penicillin, streptomycin, and bacitracin. The latter antibiotics were discovered in the author's laboratory. The volume is thoroughly documented, and an outstanding feature of the presentation is the use of illustrative cases covering the three distinct periods of therapy. One readily appreciates in studying these case reports the importance of the integration and positive correlation of a bacteriological laboratory with a surgical service.

Of especial interest is the discussion of surgical infections of the genital and urinary tracts, more especially pelvic and puerperal infections. It may be remembered that Dr. Meleney made a classic contribution to puerperal sepsis in presenting, some twenty years ago, the results of his epidemiologic and bacteriologic investigation of an epidemic of hemolytic streptococcus puerperal fever in a New York maternity hospital. His recommendations, made at that time from a prophylactic and preventive standpoint, have aided in diminishing or eliminating such outbreaks.

The volume is highly recommended.

PHILIP F. WILLIAMS.

The authors feel that, in view of the great increase in the therapeutic use of blood and its derivatives, and the steady growth in the number of blood banks, there should be a text to cover the subject in its entirety. DeGowin, Hardin, and Alsever offer in this volume, *Blood Transfusion*,<sup>28</sup> a text for those whose patients receive transfusions, those who supervise the services, and those who perform the tests and necessary procedures. The first eight chapters are devoted, one might say, to clinical considerations. The remainder, and a much larger portion of the text, discusses the technical aspects.

Emphasis is laid on the various aspects of whole-blood transfusions because as clinicians the authors consider that whole blood is the major need in the treatment of patients, and that the great majority of patients who need blood require erythrocytes particularly. It is of interest that, in 1818, James Blundell, an English obstetrician, revived the procedure of transfusion and advocated its use in the treatment of acute obstetric hemorrhage. He insisted that human blood was more effective than that of animal origin, and his writings probably introduced the subject to the American profession.

After a short historical perspective, the therapeutic choice and the merits of products for use intravenously are discussed. In the section on the immunology of blood, the various

<sup>27</sup>*Clinical Aspects and Treatment of Surgical Infections*. By Frank Lamont Meleney, M.D., F.A.C.S., Associate Professor of Clinical Surgery, College of Physicians and Surgeons, Columbia University; Associate Visiting Surgeon, Presbyterian Hospital, New York City. 782 pages with 282 illustrations. W. B. Saunders Company, Philadelphia and London, 1949.

<sup>28</sup>*Blood Transfusion*. By Elmer L. DeGowin, M.D., Associate Professor of Internal Medicine, State University of Iowa, Director, Blood Transfusion Service, University Hospitals, Member of the Committee on Blood and Blood Derivatives, National Research Council, Member of the Advisory Board for Health Services, American National Red Cross, Secretary of the Subcommittee on Blood Substitutes, National Research Council, 1940-1945; Robert C. Hardin, M.D., Assistant Professor of Internal Medicine, State University of Iowa, Formerly Senior Consultant in Blood Transfusion and Shock in the European Theater of Operations, U. S. Army, and Commanding Officer of the ETO Blood Bank; and John B. Alsever, M.D., Senior Surgeon, U. S. Public Health Service, Chief, Professional Standards, Hospital Division, U.S.P.H.S., Director of the Syracuse University Blood Transfusion Service, 1942-1944, Director of the Civilian Blood Donor Service and Associate National Medical Director, The American National Red Cross, 1944-1946. 565 pages, illustrated with 200 diagrammatic drawings. W. B. Saunders Company, Philadelphia and London, 1949.

the authors who, in keeping with the attitude shown throughout the volume, look askance at any observations not based upon experiments performed with *pure* substances!

The final chapter by the same two authors treats of the hormonal control of lactation by the prepituitary, adrenal, thyroid, and ovaries without real clarification.

This volume is a major contribution. It contains an immense amount of information, accessible through a good index. It collates and sifts scattered observations and presents them through the eyes of well-qualified specialists. The subjects dealt with are still in too labile a stage to allow us to consider this work as a definitive source book. R. T. FRANK.

**Natural Products Related to Phenanthrene,**<sup>24</sup> by Fieser and Fieser, is a third edition since 1936. Although a strictly chemical book issued as a monograph of the American Chemical Society, it is a source book indispensable to anyone doing steroid research, including research on the sex hormones, adrenal, etc. The authors emphasize that stereochemical configurations have been completely clarified. There is so much new material to be dealt with that several older sections have had to be omitted in spite of which the book has assumed double its previous proportions. They essay to systemize the bewildering steroid nomenclature.

The subjects dealt with are the quinones, morphine and related alkaloids; resin acids; sterols and bile acids; sex hormones; adrenal cortical hormones; steroid metabolism; cardiac active principles; steroid saponins, steroid and terpenoid alkaloids and stereochemistry (written by Richard B. Turner). Therefore, in spite of the mainly chemical aspects, much is of direct interest to the physician.

The authors mistakenly credit Aschheim and Zondek with the discovery that estrogenic material is present in the urine (Aschheim and Zondek, 1927). Actually the credit for discovering this most important source for obtaining purified female sex hormones belongs to Loewe and Lange in 1926. A great deal of information of interest in connection with endocrinology will be found within the pages of this important contribution. R. T. FRANK.

**Clinical Endocrinology for Practitioners and Students,**<sup>25</sup> by Martin and Hynes, is a short monograph which aims to limit itself to the well-authenticated requirements in endocrinology and to indicate the limitations of hormone therapy. It is a simple, well-arranged and well-planned description of the anatomy and physiology of the glands and includes the hormones secreted by them as well as their various effects. A special chapter is devoted to Fröhlich's syndrome and obesity. The various glands are taken up seriatim as are the breasts, and a chapter is devoted to hormonal implants. The exposition is short and accurate, more than a mere syllabus but too brief for a textbook. R. T. FRANK.

**Essentials of Gynecologic Endocrinology,**<sup>26</sup> by Riley, appears to be a student manual used at the University of Michigan Medical School. It is printed in offset but is very well carried out so that it is almost as easy to read as ordinary print. This is a well-arranged detailed lecture syllabus with some instructive graphs. The monograph is arranged in three sections—endocrine physiology, clinical and diagnostic procedures, sex-hormone chemistry and endocrine preparations. The laboratory descriptions are rather sketchy and the bibliography is somewhat haphazard. R. T. FRANK.

<sup>24</sup>**Natural Products Related to Phenanthrene.** By Louis F. Fieser and Mary Fieser, Department of Chemistry, Harvard University. Third Edition of the monograph previously entitled "Chemistry of Natural Products Related to Phenanthrene," by L. F. Fieser. 704 pages. Reinhold Publishing Corporation, New York, 1949.

<sup>25</sup>**Clinical Endocrinology for Practitioners and Students.** By Laurence Martin, M.D. (Camb.), F.R.C.P. (Lond.), Physician to Addenbrooke's Hospital, Cambridge; and Martin Hynes, M.D. (Camb.), M.R.C.P. (Lond.), Reader in Medicine in the University of Cambridge. Foreword by Sir Lionel Whitby, C.V.O., M.C., M.D., F.R.C.P., D.P.H., Regius Professor of Physics, University of Cambridge. With 8 plates and 22 text-figures. 222 pages. The Blakiston Company, Philadelphia, Toronto.

<sup>26</sup>**Essentials of Gynecologic Endocrinology (With Sections on the Male).** By Garner M. Riley, Ph.D., Assistant Professor of Obstetrics and Gynecology, University of Michigan Medical School. 205 pages. Caduceus Press, Ann Arbor, Mich., 1948.

the use of chemotherapeutic agents and antibiotics has made hemorrhage and shock the leading cause of maternal deaths. The subject is discussed from the clinical sense since obstetrical shock differs in no respect from that resulting from hemorrhage or trauma. The changes in circulatory physiology in pregnancy are discussed and followed by a description of the pathology and the factors, eleven in number, which the author states most frequently underlie the condition. The syndrome of concealed accidental hemorrhage is compared with the crush syndrome described during the blitz in Britain. The author feels that, although there are some similarities, further studies are needed to clarify this problem. There are also sections on shock in the fetus and the newborn, from trauma as well as other conditions.

Practically all agents currently used in anesthesia, the effects of preanesthetic agents, and the circulatory effects of curare are itemized in the chapter on circulatory failure from anesthesia. The author stresses the significance of anoxia in anesthesia in relation to circulatory failure. The constitutional factors in relation to pathogenesis are thoroughly taken up in the chapter entitled "The Circulatory Weakling." In this very interesting section, the problems of aging and of individualization as to operability are brought out. The final chapter discusses the treatment of shock and other forms of circulatory failure. Each section brings out very definitely and concisely the therapeutic measures which may be of value.

The volume is an outstanding presentation of the subject, and is highly recommended to the readers of this JOURNAL for the extended discussion relating to obstetrics and gynecology and the newborn.

PHILIP F. WILLIAMS

The sixth edition of Sir Arthur Keith's *Human Embryology and Morphology*<sup>30</sup> has now appeared. The first edition appeared in 1901, the fifth one in 1933. The present volume has grown to 690 pages with 575 figures. The introduction by the author is a mellow, broad-minded, and unpedantic review of the many changes in outlook, not only in embryology but in all branches of its allied sciences, which have taken place in the last forty-eight years. He states that he "still maintains that embryology becomes a profitable study only when we interpret its events in the light of evolution." This point of view predominates throughout the book. He emphasizes the profound changes in our point of view and knowledge derived from the discovery of the hormones, in embryology particularly as evocators and inductors. When the first edition was written, Germany formed the center of embryological and morphological research. This was soon transferred to the United States by the outstanding work of Franklin P. Mall and the development of the Department of Embryology of the Carnegie Institute of Washington. After Mall's death in 1917, the good work has been carried on by Streeter and now by Corner. A number of new chapters have been added by the division of old chapters, mainly those pertaining to the urogenital systems as well as those dealing with the development of the limbs, especially the growth and ossification of the human skeleton. In recent years the study of the earliest stages of the primate ovum development and the origin of the special embryonic structures and "presumptive areas" of the embryonic shield progressed. In this work, experimental embryology has by necessity been mainly confined to references. A tremendous amount of information has been tucked away in the chapter notes and references.

The book may, as heretofore, be considered a very standard, well-balanced, and detailed description of embryology. The presentation throughout is lucid and simple. It gives an impression of unhurried contemplation so often wanting in many modern books. As in other works on embryology, the origin of the ova, which to me has always held a peculiar fascination, is dealt with in a stepchild fashion. The author declares that the aberrant germ cells are no longer considered as a basis of teratomas. A very detailed index containing both subject and authors completes this very valuable textbook.

R. T. FRANK.

<sup>30</sup>*Human Embryology and Morphology*. By Sir Arthur Keith. Sixth Edition (revised and enlarged). 690 pages. The Williams & Wilkins Company, Baltimore, 1948.

groups, types and phenomena of agglutinations are described. Two chapters are devoted to the Rh-Hr blood types and isosensitization. The authors have attempted to simplify the veritable mosaic of antigens which are transmitted from parent to offspring by chromosomal combination. In the discussion of isosensitization and transfusion, the authors have fully developed the subject as it is seen in obstetric practice, and have given an excellent presentation of the many angles of this disturbing obstetrical problem. In the prevention of erythroblastosis fetalis no mention is made of the recently proposed use of hapten. This section might well be read by obstetricians, since practically every complication regarding the mother and fetus has been brought out, immunology, prognosis, diagnosis, and treatment. The collected studies from the literature on congenital malformations in erythroblastic infants suggest to the authors that isosensitization in the mother has some causal relationship to the fetus.

The succeeding four hundred pages of the book are devoted to laboratory procedures, the technique of transfusion of whole blood, the preparation and administration of plasma, of blood derivatives and of plasma substitutes. While this section is probably most useful to the physician who supervises transfusion services and to the laboratory technicians who perform the tests necessary, yet many sections, such as the discussion of transfusion complications in the recipient, transmission of disease, and possible accidents to the donors, merit attention by clinicians. The illustrations in this section, made by Ballantine, solve the problem of visual presentation of a difficult subject through a series of pictures on the margins of the pages, a series of flow diagrams which perfectly correlate and illustrate the text.

There is a good chapter on transfusion services, both in the operation of a hospital blood bank and the services in civilian practice in communities, regions, or states similar to wartime services. This particular part might well be read by those who look forward to a catastrophic calamity in civilian practice, or to a future atomic war. The final chapters, well illustrated, describe the necessary equipment and the preparation of apparatus and fluids for parenteral therapy.

A tremendous amount of material has been brought together in this book which is thoroughly documented and unusually well illustrated. Surely those who are concerned with blood transfusions or the use of blood substitutes should find much to help them in the problems of this mode of therapy.

PHILIP F. WILLIAMS.

This monograph, *Shock and Allied Forms of Failure of the Circulation*,<sup>20</sup> by H. A. Davis, discusses exhaustively the various phases of the topic. Since acute failure of the circulation is met in practically every field of clinical practice, it follows that a book of this nature should be of great value in many lines. The logical arrangement of the contents carries the discussion from the author's excellent definition of shock and the various classifications which have been offered through the methods of diagnosis of shock, from trauma and hemorrhage, infections, failures of nutritional origin, and in individuals at the extremes of life.

The author gives an explanation of the origin of circulatory failure as well as an extended discussion of the physiological changes not only in the heart and vessels but in the various systems as well, and brings out very understandably the biochemical changes which are followed by the degeneration in organs and systems. There is an excellent discussion of irreversible shock.

Of particular interest to the readers of this JOURNAL should be the extended discussion on obstetrical shock. The author describes acute circulatory failure of obstetrical origin which may occur before, during, or after labor. He notes that better care and early detection have reduced the toxemia death rate and that better control of puerperal infections by

<sup>20</sup>*Shock and Allied Forms of Failure of the Circulation*. By H. A. Davis, M.D., C.M., F.A.C.S., Associate Professor of Surgery, Director, Division of Surgery, Graduate School of Medicine, College of Medical Evangelists, Los Angeles Division; Senior Attending Surgeon, Los Angeles County General Hospital and White Memorial Hospital; Visiting Surgeon, Cedars of Lebanon Hospital and California Hospital. 576 pages with 55 illustrations. Grune & Stratton, New York, 1949.



Carcinoma of the vulva is taken up and emphasis is placed on the early removal of precancerous lesions such as kraurosis and leucoplakia. Finally, in this chapter, pre- and postoperative care in gynecology is described. The final fourteenth section deals with physical and chemical agents, including burns, poisons, bites of insects and reptiles.

This very ambitious volume varies greatly in different sections. It certainly should prove of real use to pick up when confronted by conditions with which the physician is unfamiliar. It will perhaps lead him to the correct paths in further study of the situation.

R. T. FRANK.

**The Pharmacologic Principles of Medical Practice,**<sup>32</sup> by Krantz and Carr, is a textbook on pharmacology and therapeutics designed by the authors for medical students, physicians, and members of the professions allied to medicine. The average medical student will find the book a bit above his head. The arrangement is simple, consisting of nine parts. The introductory portion deals with the history of pharmacology, pharmacologic principles, and an introduction to drugs which includes the pharmacopoeia, prescriptions, methods of administration, and a description of the response of cells to drugs.

The subsequent parts include the anti-infective drugs, the response of the skin and mucous membranes, the response of the central nervous system to drugs. The latter include depressants such as alcohols, anesthetics, opium and its alkaloids, addictive analgesics and marihuana; the problems of drug addictions and then a description of the various depressants such as the barbiturates, etc., etc., as well as hypnotics and antipyretics; finally, the central nervous system stimulants.

Part V deals with the response of the autonomic nervous system covering both the stimulants and depressants of the sympathetic and parasympathetic system. Ganglionic depressants and response to histamine and antihistaminics are taken up. The next portion deals with the heart and circulation.

I read with particular care Part VII which covers the reproductive system. This deals with ergot and posterior pituitary for the uterus; gonadotropins, estrogen and progesterone, and androgens. The subject is well handled and well covered from the historical and the purely chemical, as well as the pharmacological and clinical sides.

Part VIII covers the effects of pharmacological agents on metabolism which includes water balance, renal threshold, carbohydrate metabolism in insulin, iodine metabolism, and, finally, calcium-phosphorus metabolism as affected by calciferol and the parathyroid hormone.

The chemical aspect is fully emphasized. Most chapters end with a chart of the official prescriptions and dosages and a short chapter bibliography confined largely to the most recent literature. A number of full-page photographs of well-known pharmacologists, both past and still present, adorn the volume. At the end there is a series of typical prescriptions covering various conditions.

R. T. FRANK.

Dr. Joseph H. Barach offers this book, **Diabetes and Its Treatment,**<sup>33</sup> to the general medical man as a clinical approach to an understanding of diabetes and its treatment. He states that there are more than one million potential diabetics in the United States, and that diabetes can be the most scientifically treated of all diseases. The control of the measurable factors in the disease requires, however, he states, knowledge and the total effort of the doctor, the nurse, a capable dietitian and most of all a cooperative patient.

<sup>32</sup>**The Pharmacologic Principles of Medical Practice. A Textbook on Pharmacology and Therapeutics for Medical Students, Physicians, and the Members of the Professions Allied to Medicine.** By John C. Krantz, Jr., Professor of Pharmacology, School of Medicine, University of Maryland, Secretary of the General Committee of Revision of the United States Pharmacopoeia; and C. Jelleff Carr, Associate Professor of Pharmacology, School of Medicine, University of Maryland, Auxiliary Member of the Revision Committee of the United States Pharmacopoeia. 980 pages. The Williams & Wilkins Company, Baltimore, 1949.

<sup>33</sup>**Diabetes and Its Treatment.** By Joseph H. Barach, M.D., F.A.C.P., Associate Professor of Medicine, University of Pittsburgh; Senior Medical Staff, Presbyterian Hospital; Chairman, Metabolism and Endocrinology Study Section, Research Grants Division, U. S. Public Health Service (1946-1951). 316 pages with 78 figures, many tables, and 317 diet schedules. Oxford University Press, New York, 1949.

**Current Therapy—1949,**<sup>31</sup> which contains the latest approved methods of treatment for the practicing physician, is a large, 672-page volume arranged somewhat in encyclopedic fashion. The editor, Howard F. Conn, has enlisted twelve prominent physicians as consulting editors, and over two hundred contributors from various fields, who were selected mainly by these consultants. In addition, the editor apparently has had to act as pinch hitter in many instances because there are very few sections which do not contain articles from his pen. The book is written with the presumption that the diagnosis has been established. This enables the therapy to be presented in very short order. In many instances the methods recommended by several authors are given without prejudgment and presented in the alphabetical order of the authors' names. There are fourteen sections, each with its separate table of contents. In addition there is a good index of both subjects and authors.

For the purpose of review it is impossible to go into complete detail. I have reviewed it from the standpoint of a man who selects a number of subjects, upon the treatment of which he wants to inform himself. In the section on infectious diseases, the editor, Howard F. Conn, covers twenty-one of the forty subjects himself. It is impossible to judge just when the "books were closed." However, it may have been some months ago because there is no "specific remedy" for psittacosis or for typhoid. However aureomycin is mentioned for brucellosis. The next section is on the digestive tract. In the treatment of appendicitis, the methods of three surgeons are described. All important phases of the digestive system are gone into. Section 3 is on diseases of metabolism and nutrition. Section 4 deals with diseases of the endocrine system. In this, only a certain number of diseases have been selected for discussion. The fifth section covers the diseases of the urogenital tract, which is unusually complete. The venereal diseases are contained in Section 6. Three methods of treatment of syphilis in pregnancy are taken up. The succeeding section covers allergy. Section 8 pertains to the diseases of the skin and like the section on urology, is very complete. Diseases of the respiratory system are in Section 9. Section 10 contains diseases of the cardiovascular system; Section 11, those of the blood and spleen. Diseases of the nervous system are taken up in Section 12. In my mind there is a question whether the general practitioner will obtain much help on the rather elaborate therapy of brain tumors.

Section 13 is of particular interest to our readers as it covers obstetrics and gynecology in 53 pages. The section begins with antepartum care. In threatened abortion, I am surprised to find no mention of the high estrogenic therapy when the danger of interruption of early pregnancy appears likely. I cannot agree that "needling of the cul-de-sac for diagnosis by the general practitioner capable of minor surgery" would be a safe recommendation. There are two contrasting methods for treatment of the various forms of toxemia of pregnancy described. Cesarean section, analgesia and anesthesia in obstetrics, postpartum hemorrhage and postpartum care are taken up sequentially. The functional bleeding of endometrial hyperplasia is treated very cavalierly and could stand considerable expansion. Curettage, curettage and radium, and hysterectomy are mentioned without elaboration. The giving of estrogens in large doses for three or four days is likewise recommended, a length of treatment entirely inadequate, in my opinion. The paragraphs on female sterility are detailed and good. The treatment of bilateral cystic ovaries by surgery alone appears radical to me. Further on, menopause and vaginal infections are dealt with. I am surprised to find mammary substance still recommended as part of the medical treatment of fibroid tumors. Tumors of the ovary in the pregnant and nonpregnant women are described. I was somewhat shocked to find the statement that carcinoma of the cervix is more common in ward patients and carcinoma of the endometrium in private patients! For the treatment of carcinoma of the cervix, one author emphasizes radical operation; the other, the more current treatment by radiotherapy.

<sup>31</sup>**Current Therapy—1949. Latest Approved Methods of Treatment for the Practicing Physician.** Howard F. Conn, M.D., Editor. Consulting Editors—M. Edward Davis, Vincent J. Derbes, Garfield G. Duncan, Hugh J. Jewett, William J. Kerr, Perrin H. Long, H. Houston Merritt, Paul A. O'Leary, Walter L. Palmer, Hobart A. Reinmann, Cyrus C. Sturgis, Robert H. Williams. 672 pages. W. B. Saunders Company, Philadelphia. 1949.

In the final part of the book, the changing attitudes on sex in our present social order are discussed, and are followed by statements as to prostitution and venereal disease. The incompatibilities of marriage and the divorce question are analyzed. The regression of the sexual life in men and women is dealt with in a discussion of the climacteric. The ability of women to take part in extramarital professional life, civic responsibilities, and other activities is clearly shown to be more than a working possibility. The place of the family in the community, the strength of individual family life, what the parents could and should give in the way of education, not only in family life, but also for their children's lifework, are well presented.

This book is full of accurate information, thoughtful discussion, and ably considered solutions of almost every problem of married life. It is written by men and women who are outstanding in their fields of endeavor. The book should be equally valuable on the desk of the family doctor, the marriage counselor, or the specialist or in the library of the homes of men and women who are eager to make of their marriage a secure and well-adjusted family unit in the community.

PHILIP F. WILLIAMS.

Dr. Abner I. Weisman offers his opinion on what *The Engaged Couple Has a Right to Know*<sup>25</sup> in his guide to happy marriage. As Dr. Abraham Stone says in a foreword to the book, there have been rapid and forward social changes reflected in family relations in recent years. Young people who, in their new freedom, select their marital partners, have not only the opportunity for independent actions but also new ideas and responsibilities. To provide guidance and counsel, information and interpretation in these new responsibilities, Dr. Weisman presents a book to provide information and insight into the problems of engagement and early marriage. The physiology of youth and maturity is the basic theme of his early chapters on the motivating forces which lead to marriage. He utilizes the topics of anatomy and physiology, social implications of the engagement period, the physical health, and the premarital and preconceptional examinations, to emphasize the eugenic aspect of marriage. Again, the psychic side of the sex relation, the actual consummation of marriage, and the use of birth control are discussed in portraying the early days of a marriage. The successful consummation of marriage, pregnancy with psychic changes, and the arrival and reception into the home circle of the new baby, offer an opportunity for the author to advise on the frequent problems of the new triangular human relationship.

The volume in its easily understood presentation should serve to meet the needs of many for frank and skilled counsel in preparation for marriage.

PHILIP F. WILLIAMS.

In his book, *Sex and You*,<sup>26</sup> Dr. LeMon Clark gives us a frank, easily understandable and well-presented discussion on the influence of sex in our lives. As to sex education, he feels that the average child has formed all of his basic attitudes by the time he is five years old, and that many of the incorrect attitudes and marital difficulties arise from a lack of truthful, honest explanations of sex in these almost infant years. Dr. Clark feels strongly that the social heritage of misinformation pursues an individual throughout life, and is the origin of many mistaken attitudes of later years. The discussion of the teenage years of both boys and girls is excellent. Marriage relationship and customs are wisely examined while the subjects of pregnancy, infertility, and birth control are ably presented. The author's attitude toward divorce is broad-minded. The final chapter evaluates briefly some normal and distorted conventions and conditions, and the place of psychoanalysis in the frequent deviation of sexual relations.

<sup>25</sup>*The Engaged Couple Has a Right to Know.* By Abner I. Weisman, M.D., Assistant Visiting Gynecologist and Obstetrician, Metropolitan Hospital; Associate Attending Gynecologist and Research Associate in Pathology, Jewish Memorial Hospital, New York, N. Y. 252 pages with 14 illustrations. Renbault House, New York, 1948.

<sup>26</sup>*Sex and You.* By LeMon Clark, M.S., M.D. 205 pages. The Bobbs-Merrill Company, Indianapolis, New York. 1949.

The early portions of the book take up the history and a description of the disease and its background. The laboratory methods essential in diagnosis and treatment are set forth at length. A full discussion of the complications of this disease show the many pitfalls in its control, while an entire chapter is devoted to the circulatory complications.

Dr. Barach has given two excellent chapters on surgery in diabetes and on pregnancy in the diabetic. In the latter chapter he states that one out of six patients who are pregnant and diabetic has developed the disease during pregnancy. He contrasts the results obtained in the preinsulin and insulin regimes. He feels that cesarean section is the optimum method of delivery. White's principles in handling pregnancy in diabetics are elaborated upon, and schedules are presented for hormonal substitution therapies, diets during pregnancy, and detailed instructions for the last month of pregnancy, the prepartum or preoperative routine and postpartum care. He also discusses in this chapter the subjects of excessive insulin in the newborn and the care of the premature infant born of a diabetic mother.

The pharmacology of insulin in its various forms is described and the physiologic and therapeutic effects, as well as complications attendant upon its use, are taken up. The book is replete with detailed schedules of instructions for nurse, dietitian, and patient. Following a statement of nutrition in general and diet of the diabetic in particular, the author includes a section on diets, calorie values, diets for men under various categories, and for women and children. He gives a long list of emergency diets which may be suitable in complications, and there are many pages of recipes.

The complete discussion of this common and increasing disease, the excellence of the presentation, and the directions not only for the internist and his associates but also for surgeons, obstetricians, and public health officers, including the police, make this book a valuable contribution.

PHILIP F. WILLIAMS.

This book, *Successful Marriage*,<sup>34</sup> is an exceptionally fine presentation of the many problems of marriage and their proposed solutions. The editors, Drs. Fishbein and Burgess, chose thirty-eight outstanding and distinguished specialists to contribute chapters, and have arranged the material in the following broad divisions: preparation for marriage, the marriage, reproduction, the child in the family, and the social problems of sex and marriage. The division of the material and its assignment to its various contributors have been wisely made. We find in the first part a discussion of the selection of a husband or a wife, premarital sex relationships and the reasons for premarital and preconceptional examinations, and a chapter which answers most of the questions which the about-to-be-married couple may propose to the marriage counselor, be he psychologist, family physician, or gynecologist.

The second division, on the marriage, discusses frankly and in detail the sex aspects of the relationship, as well as the more practical personal and family problems of home management and finance. One also finds here a discussion of the various factors which produce marital maladjustments, and a discussion of miscarriages and abortions.

There are chapters on heredity and infertility, as well as the hygiene of pregnancy, and a description of labor in the third section of the book, and this part includes also a short statement on the prevention of conception and the commonly used methods, which are illustrated. The physical and mental growth of the child is well described, and there is an informative section on the subject of adoption, and another on the psychology of remarriage and the relationship of stepchildren in the family. Further growth of the child from the physical, sexual, and psychological aspects of development, and the preparation during adolescence for a successful marriage for the children in the family are included.

<sup>34</sup>*Successful Marriage, an Authoritative Guide to Problems Related to Marriage From the Beginning of Sexual Attraction to Matrimony and the Successful Rearing of a Family.* Edited by Morris Fishbein, M.D., editor, *Journal of the American Medical Association* and *Hygeia, the Health Magazine*; and Ernest W. Burgess, Ph.D., Professor and Chairman, Department of Sociology, University of Chicago. 515 pages, illustrated. Doubleday & Company, Inc., Garden City, N. Y., 1948.

## Correspondence

### Diethylstilbestrol Dosage in Threatened and Habitual Abortion and Premature Labor

*To the Editor:*

Dr. O. Watkins Smith's paper on "Diethylstilbestrol in the Prevention and Treatment of Complications of Pregnancy" (AM. J. OBST. & GYNEC. 56: 821, 1948) was read with a great deal of interest, especially the part about the dosage of stilbestrol. I have been trying for about ten years to find the correct dose of stilbestrol in threatened and habitual abortion and premature labor.

Most interesting to me were the following statements: (1) "15 cases [threatened abortion] on too high dosage, 4 of whom aborted." (2) "Of the 28 women who were given what we would consider an overdosage, only 17, or 61 per cent, carried." (3) "We have considered the dosage too high if 10 mg. or more are given daily for more than 10 consecutive days before the sixth week, 25 mg. or more daily before the tenth week, 50 mg. or more before the fifteenth week and 100 mg. or more before the twentieth week."

It has been found that the dose of stilbestrol varies in each individual. The amount of stilbestrol required is that amount that stops cramps, spotting, bleeding, and/or pain and keeps them from returning. The original dose may be from 25 to 1,000 mg. The dose required to keep these signs and symptoms from recurring is usually  $1\frac{1}{2}$  grain (10 mg.) to  $1\frac{1}{2}$  grains (100 mg.) daily. Most patients require 25 to 50 mg. ( $\frac{3}{8}$  to  $\frac{3}{4}$  grains) every morning. We have been unable to make up a table of doses in these conditions, and we have tried to for years.

As soon as the patient begins to abort, regardless of the week of pregnancy, 10 to 25 mg. micronized stilbestrol tablets are given immediately and 4 25-mg. tablets are given every 15 minutes until all signs and symptoms have stopped. Then 2 25-mg. tablets three times a day and at bedtime for one week, one 25-mg. tablet three times a day and at bedtime for one week. Then 50 mg. every morning on rising. In 24 to 48 hours the patient comes to the office and 10 c.c. (25 mg. per c.c.) of micronized stilbestrol are given intramuscularly twice a week for four to six doses. This aids in saving more threatened abortion cases. Two hundred fifty milligrams of stilbestrol intramuscularly as soon as possible after a patient begins to abort are a very valuable adjunct in the treatment of threatened abortion. The dose is not increased as term is approached. Regardless of the dose we have been unable to cause any patient to abort or produce any sign or symptom of abortion with doses that are many times (even a thousand times) more than those advocated by Dr. Smith, given in her table of dosage. The daily dosage of 5 to 1,000 mg. at any stage of pregnancy did not produce any harm to the pregnancy, mother, baby, placenta, nor was any harm shown by repeated weekly complete laboratory studies. We have given pregnant patients very large amounts of stilbestrol during pregnancy up to 120,730 mg. without producing any signs or symptoms of an abortion.

It has been my observation that the larger the daily dose, the surer the patient will be to carry the baby to term and deliver a normal baby. Also it requires a much larger daily dose of stilbestrol as the number of abortions which had occurred rises. In one patient who had lost thirteen babies, it required 77,040 mg. during the entire pregnancy to hold the fourteenth baby. In an habitual aborter who had lost six babies, it required approximately 30,000 mg. to carry the baby to term.

In premature labor it has been found that it requires 200 or more mg. daily of micronized stilbestrol to keep patients from aborting if they begin to have labor pains. To prevent possible premature labor from occurring again, 50 mg. daily are given up to the eighth month.

The manner in which the book is written recommends it to the lay public and to those who are called upon to advise on the attitudes and functions of sex.

PHILIP F. WILLIAMS.

**Education for Professional Responsibility**<sup>37</sup> is a report of an interprofessions conference held in April, 1948. The conference was planned by leaders in education in schools of divinity, medicine, law, engineering, and business, since it had become increasingly clear to them that the major problems of professional education in these branches were common, and that unusual opportunities for fruitful discussion of such problems could be provided by a variety of experience of teachers in these different professions. The papers which constitute the formal portion of the conference are herewith published.

They deal with the objectives as well as the content and the method in such education. The changing concepts of objectives are historically developed, and it is interesting to follow the steps in professional education which now lead to a general acceptance of the case system in all five of the interested professions. Dr. James H. Means emphasizes this system in medical education in his discussion of the clinical clerkship which, he says, actually amounts to an apprenticeship. Dr. Means says that one of the problems of medical education is how to make the scholarly attitude persist through life, how to insure that the physician and surgeon will continue professional, not lapse into the merely vocational or commercial. Miss Eleanor Cockerill continues the subject of the conduct of medical education in discussing the relationship of social and environmental factors to medicine. A medical student, she feels, must be taught the relationship of these factors to medicine and must be helped to develop an ability to use this knowledge both in actual care of patients and in assuming a professional responsibility within society.

In the material presented in the final session on social and humanistic aspects of professional education these two factors are again referred to in connection with the problems of psychology and psychiatry. Dr. John Romano stresses that the trends and practices in current medical education may possibly develop in the medical student a one-sided, essentially physicochemical concept of human biology.

It would appear that many problems are common to these five professions and solutions by one branch of teaching may well be considered by the teachers in other lines. A reading of this small volume should make professional education in any branch more effective.

PHILIP F. WILLIAMS.

Just why a copy of the **Archives of Pathology**<sup>38</sup> from Lisbon arrived now when the number is dated December, 1941, I am unable to state. The number contains varia, has résumés in French, occasionally in German and English. There is an article on 439 cases of cancer of the cervix; another on isolation of the pertussis germ for diagnosis, in which 96 per cent of 167 cases gave positive reactions as they were encountered in the first week. The illustrations are excellent.

R. T. FRANK.

<sup>37</sup>**Education for Professional Responsibility.** A report of the Proceedings of the Inter-Professions Conference on Education for Professional Responsibility held at Buck Hill Falls, Pa., April 12, 13, and 14, 1948. 203 pages. Carnegie Press, Carnegie Institute of Technology, Pittsburgh. 1948.

<sup>38</sup>**Arquivo de Patologia.** Órgão do Instituto Português de Oncologia. Vol. XIII, No. 3. December, 1941. F. Gentil e M. Athias, Palhavã, Lisboa.

## Items

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### International Congress on Obstetrics and Gynecology

The committee on Clinics of the International and Fourth American Congress on Obstetrics and Gynecology is composed of the following:

Canada	Dr. Edwin Robertson, Kingston, Ontario
New England	Dr. Duncan Reid, Boston, Mass.
Central Northeast	Dr. Nicholson J. Eastman, Baltimore, Md. (Seaboard cities, Washington to N. Y. inclusive) Dr. Clyde L. Randall, Buffalo, N. Y. (exclusive of New York and Washington, D. C.)
South	Dr. H. Hudnall Ware, Richmond, Va.
Midwest	Dr. John L. McKelvey, Minneapolis, Minn. (Minnesota, Wisconsin, and Iowa) Dr. John I. Brewer, Chicago, Ill. (Missouri, Indiana, Illinois, Ohio, and Michigan)
Central Northwest	Dr. Edward S. Taylor, Denver, Colo.
Southwest	Dr. Conrad Collins, New Orleans, La.
Pacific Coast	Dr. Charles E. McLennan, San Francisco, Calif.

The Committee on Clinics plans, by September 1, to have information on the current, up-to-date activities all over the United States and Canada, in order to direct men: (1) whose travel plans are flexible, to the leaders in a given field of endeavor; and (2) those whose travel plans are fixed, to activities along their respective routes of travel.

In addition, the Committee plans to have in its possession information on various medical centers planning special demonstrations, wet or dry clinics, and exhibitions of research. Such information will include both: (1) the time and place of such demonstrations or exhibitions and (2) the number of visiting physicians who can be accommodated at a given place and time.

Finally, the Committee on Clinics plans to have a sort of travel routing agency so that if any visiting physician sends a list of subjects he wishes to observe, we can route him, either before or after the Congress, by way of the best possible places for satisfying his desires.

Inquiries should be directed to Mr. Karl S. Richardson, 24 West Ohio Street, Chicago, Ill.

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### American Board of Obstetrics and Gynecology, Inc.

The annual meeting of the Board was held in Chicago, Ill., from May 8 to May 14, 1949, at which time 236 candidates were certified.

New Bulletins, incorporating changes made at the recent meeting, are now available for distribution upon application and give details of all new regulations.

The next scheduled examination (Part I), written examination and review of case histories, for all candidates will be held in various cities of the United States and Canada on Friday, Feb. 3, 1950. Application may be made until Nov. 5, 1949. Application forms and Bulletins are sent upon request made to

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY,  
1015 HIGHLAND BUILDING,  
PITTSBURGH 6, PA.

In conclusion, the larger the daily dose of stilbestrol, the surer the patient will be to carry the pregnancy to term and have a normal baby. It is impossible to abort a woman with stilbestrol regardless of the daily initial dose of 500 mg. or total dose of 120,730 mg. during the entire pregnancy. No set table of dosage of stilbestrol has been found by me because the dose varies in each individual. The amount that does the job is the required dose.

KARL JOHN KARNAKY, M.D.

329 MEDICAL ARTS BUILDING  
HOUSTON, TEXAS  
MAY 14, 1948



## Materials and Methods

A group of solid ovarian tumors including three granulosa-cell tumors, one thecoma with granulosa-cell nests, one luteinized thecoma, six thecomas, and two fibromas were available for study. For evidence of functional activity of these tumors the patient's history was examined for clinical evidence; when available the endometrium was examined and in one case of granulosa-cell tumor, estrogen studies were done on the patient's urine. Tissue fixed in formalin for twenty-four hours or longer was used. Serial sections were cut on the freezing microtome at 15 to 35 micron thicknesses. The 15 micron sections were stained with Sudan IV. For studies of fluorescence and birefringence, sections were mounted on slides in nonfluorescent glycerine. Observations on birefringence were made with a Spencer polarizing microscope, using plane-polarized light, while a fluorescent microscope using a beam of rays obtained by filtering the light of a carbon-arc lamp through a copper sulfate solution and a Corex filter No. 586 was used in determining fluorescence. Alternate sections were placed in acetone for twenty-four hours and then mounted in glycerine and subjected to these examinations.

Since the ovarian hormones are soluble in fat solvents, any substance which, after extraction with acetone, still reacts with the above reagents should probably not be regarded as a functioning ovarian steroid. Acetone extraction prevented all the above reactions in the normal human ovary and in this group of ovarian tumors.

Cholesterol, its derivatives, and their esters frequently form birefringent crystals, as do the ovarian steroids. This property, which is caused by the radial symmetry of the steroid molecules in liquid spherocrystals, is an expression of the molecular pattern of this class of compounds (Lison<sup>2</sup>). In the rat and human ovary two varieties of birefringence have been described. One is a fibrillar type, insoluble in acetone and associated with connective tissue bundles. The other is a crystalline birefringence, soluble in acetone and present in parenchymatous cells. The observations herein reported deal only with the latter variety of birefringence.

Bierry and Gouzon<sup>4</sup> demonstrated that purified estrogenic sterols exhibit a greenish-yellow fluorescence. In the rat and human ovary the cells of the theca interna emit a yellowish-green fluorescence as do the granulosa lutein cells, but the granulosa cells of the follicle exhibit a pale blue fluorescence.

The phenylhydrazine method of Bennett<sup>5</sup> was used. Alternate sections were extracted with acetone for twenty-four hours and then submitted to the phenylhydrazine reaction. Phenylhydrazine reacts with the carbonyl group of the reactive molecules to produce a yellow phenylhydrazone which can be visualized in the sections.

Sections were also treated with concentrated sulfuric acid. They were mounted on slides and the excess water was blotted off. A drop of concentrated sulfuric acid was placed on the tissue and a coverslip dropped on immediately. Sections extracted with acetone were similarly treated. Following the addition of sulfuric acid to reacting tissue, reddish-brown droplets or granules develop within sixty seconds. This is the Liebermann-Burchard reaction applied to tissues. It has been shown that steroids which possess unsaturated linkages will give this chromogenic reaction (Fieser<sup>6</sup>).

In addition, the Schiff or plasmal reaction of Feulgen and Voit<sup>7</sup> was used in several cases instead of the phenylhydrazine reaction. The Schiff reagent consists of basic fuchsin which has been decolorized by sulfurous acid. Aldehydes and some ketosteroids contain carbonyl groups active enough to cause this reagent to develop a violet color, according to Dempsey and Wislocki.<sup>8</sup>

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## Original Communications

### HISTOCHEMICAL OBSERVATIONS ON GRANULOSA-CELL TUMORS THECOMAS, AND FIBROMAS OF THE OVARY

D. G. MCKAY, M.D., D. ROBINSON, M.D., AND A. T. HERTIG, M.D., BOSTON, MASS.

*(From the Mallory Institute of Pathology, Boston City Hospital, the Pathology Laboratory of the Free Hospital for Women, and the Departments of Pathology and Obstetrics, Harvard Medical School)*

RECENT histochemical techniques designed to indicate the cytologic localization of certain steroid hormones have been applied by Dempsey and Bassett<sup>1</sup> and McKay and Robinson<sup>2</sup> to the rat and human ovary, respectively. Steroid substances were found in the theca interna cells of the developing follicle, in the granulosa lutein and theca lutein cells of the corpus luteum and in the interstitial cells\* of the ovary. No reactive materials were found in the granulosa cells of the Graafian follicle or in the stroma cells of the ovarian cortex or medulla. Perhaps the most significant finding is the fact that in the Graafian follicle of both species steroidal substances are confined to the theca layer and are not present in the granulosa layer. This has been taken as evidence that the theca cell and not the granulosa cell is the one which produces the steroid hormone of the follicle. This idea is not a new one, since much experimental evidence in the past has indicated that it was true.

McKay and Robinson<sup>2</sup> also estimated the relative amounts of reactive materials present in the follicle and corpus luteum during the stages of development of these structures throughout the menstrual cycle. It was found that the amounts of steroid substances in the follicle and corpus luteum varied directly with the changing concentrations of urinary estrogen.

Because granulosa-cell tumors and thecomas are so frequently associated with an increased production of estrogenic hormone, and because fibromas are on occasion difficult to differentiate from thecomas, it was thought that the application to these tumors of the histochemical procedures outlined by Dempsey and Bassett<sup>1</sup> might reveal some information of theoretic and practical interest.

\*Interstitial cells are the large, isolated lipid-laden cells which are occasionally seen lying in the cortical stroma.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

Call-Exner bodies. Bands of connective tissue lay in between the tumor-cell masses. In several areas these connective tissue cells had assumed a plump, fusiform shape and had the appearance of theca interna cells.

Sudan IV stains revealed a few scattered, fine, red droplets in the granulosa cells and a large concentration in the theca-like cells of the connective tissue bundles (Fig. 1). There were no other reactive substances in the granulosa cells, but the plump connective tissue cells contained large quantities of birefringent crystals which gave a greenish-yellow fluorescence and reacted positively with phenylhydrazine and sulfuric acid.

CASE 2.—Paulkner Hospital; S48-1075. This 49-year-old white woman entered the hospital in June, 1948, with a chief complaint of vaginal bleeding for the past year. She had been spotting for this length of time with four episodes of heavy bleeding which occurred at irregular intervals and lasted for approximately three weeks. Physical examination revealed a soft, movable, midline mass rising to just above the symphysis. A total hysterectomy with removal of a right ovarian tumor was performed.

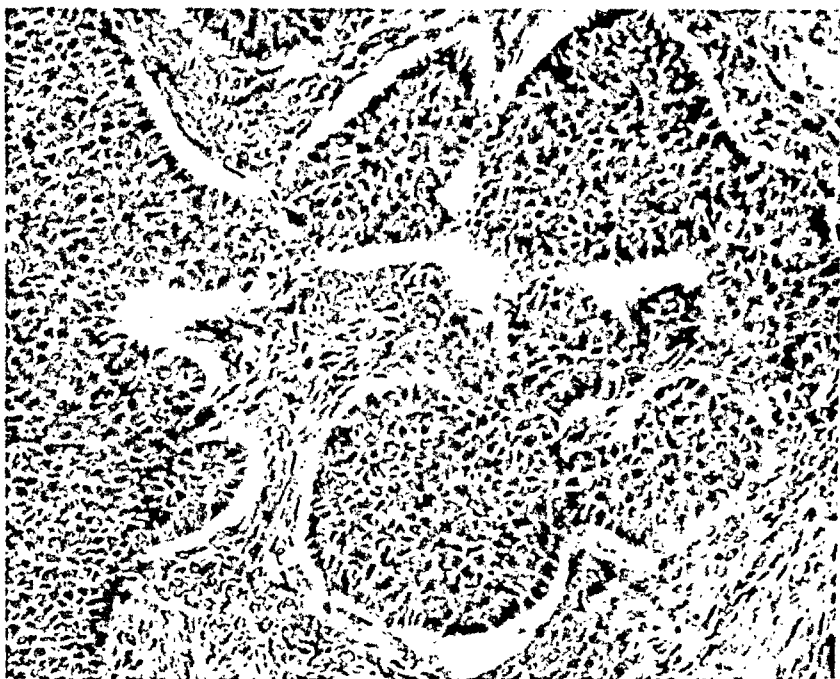


Fig. 2.—Photomicrograph of granulosa-cell tumor of Case 2. Phloxine-methylene blue stain. ( $\times 160$ )

The right ovarian mass weighed 275 Gm. and measured 11 cm. in diameter. It had a smooth, glistening surface and a central cavity. The cystic space in the center of the tumor was filled with fluid blood. The wall of the tumor measured from 0.5 to 3.0 cm. in thickness and consisted of solid, granular, pale yellow and pink tissue. The uterus measured 10 by 5.5 by 3.5 cm. and was not remarkable except for a very thick endometrium which measured up to 0.6 cm. in places. The tubes and the left ovary were not remarkable.

Microscopically the endometrium revealed a cystic hyperplasia.

Histologic sections of the tumor revealed cords and sheets of cells with round to oval nuclei arranged in palisades around the edges of the tumor-cell masses where they were in contact with the numerous bands of connective tissue. There were also numerous Call-Exner bodies in the sheets of tumor cells. The connective tissue cells were plump and fusiform and some intracytoplasmic vacuoles were observed in the section stained with phloxine-methylene blue (Fig. 2).

Histochemical studies revealed reactive materials in the large fusiform connective-tissue cells and none in the granulosa cells (Fig. 3).

Albert and LeBlond<sup>9</sup> and Gomori<sup>10</sup> have criticized the use of the phenylhydrazine reaction and the plasmal reaction as indicators of the presence of ketosteroids. These authors believe that the reactions in tissues to these reagents are due to the presence of acetals and that it is unlikely that positive plasmal reactions can be used to indicate steroids. Although Dempsey et al.<sup>11</sup> do not ascribe specificity to either the phenylhydrazine or the Schiff reaction, they do regard the Schiff reaction as one of a linked series which, taken together, provides evidence for the presence of these compounds.

In summary, any fat-soluble substance which has all these properties will have a polycyclic molecule with a double bond somewhere in the molecule and will have a carbonyl group attached to it. The ketosteroids have such a structure and give these reactions. Dempsey and Bassett<sup>1</sup> conclude that these reactions indicate the presence of certain ovarian hormones or their precursors and, more importantly, those tissues which fail to give the reactions are devoid of the steroid hormones.

## Results

### Granulosa-Cell Tumors

CASE 1.—Salem Hospital; S47-3. This 60-year-old white woman entered the hospital with a chief complaint of weakness, indigestion, and constipation. There was no history of postmenopausal bleeding. On physical examination a mass "the size of a grapefruit" was palpated in the left lower quadrant. The stool was guaiac negative and other laboratory tests were noncontributory. A laparotomy was performed. There was a large amount of bloody fluid in the abdomen. The omentum and small bowel were adherent to a friable ovarian mass which was removed manually. This was followed by severe hemorrhage. Following the operation the patient's condition became worse and she died two days postoperatively.

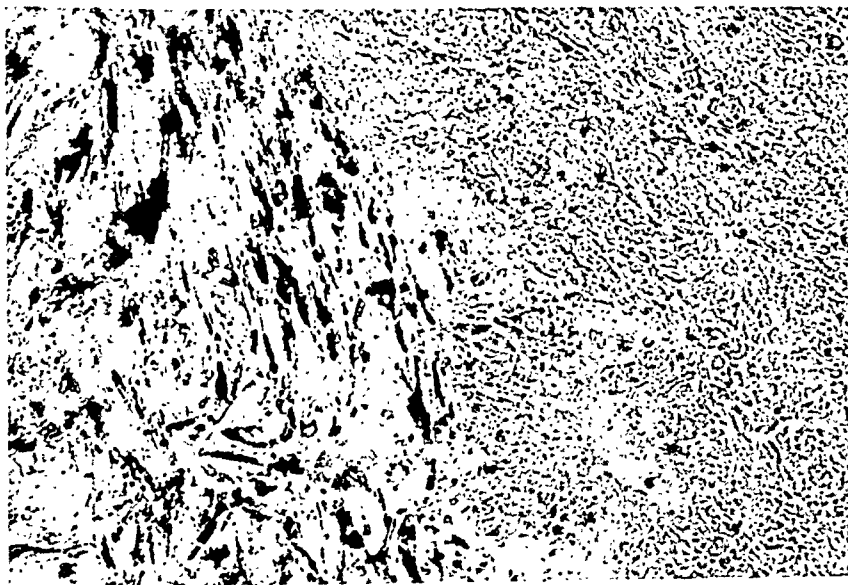


Fig. 1.—Photomicrograph of Sudan IV stain on granulosa-cell tumor of Case 1. The cellular mass on the right is made up of tumor cells with very few tiny, scattered sudanophilic droplets. The spindle-shaped, theca-like cells on the left contain large amounts of fat. These cells gave all the reactions of steroid hormones while granulosa cells were negative. (×400)

The pathologic specimen consisted of several pieces of firm, yellow-white tumor tissue associated with several small clots of blood. Microscopically, the tumor was made up of sheets and cords of small cells with round nuclei, indistinct cytoplasmic borders and occasional

with a few scattered mitotic figures. In a few areas, the cells were arranged in tiny rosettes surrounding a central mass of acidophilic granular material, thus resembling Call-Exner bodies. There was a delicate, scant stroma in the regions immediately adjacent to the numerous blood vessels (Fig. 4).

When stained with Sudan IV, a few tiny, intracytoplasmic red droplets were seen in the granulosa cells. No birefringent crystals were present in the tumor tissue and the latter tissue gave a negative reaction to sulfuric acid and Schiff's reagent. The granulosa cells gave a pale blue fluorescence. There were no sudanophilic droplets in the stromal cells, nor did they give any reactions consistent with the presence of steroid substances.

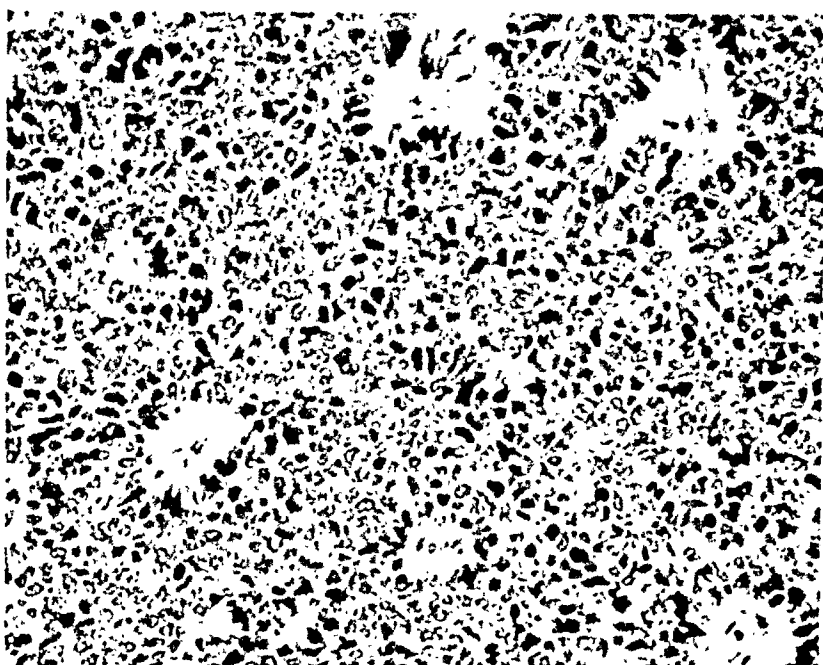


Fig. 4.—Photomicrograph of granulosa-cell tumor of Case 3. Phloxine-methylene blue stain. (X400)

## Active Thecomas

### Thecoma With Granulosa-Cell Nests

CASE 4.—Boston City Hospital; 847-3852. This 65-year-old white woman entered the hospital with a chief complaint of a mass in the abdomen which had been noticed for the past two years. She gave no history of postmenopausal bleeding. A large abdominal mass, thought to be a uterine leiomyoma, was palpated and a laparotomy performed with removal of the ovarian mass as well as the uterus, tubes, and the other ovary.

The pathologic specimen consisted of a mass measuring 22 by 17 by 16 cm. which weighed 3,800 Gm. It had a smooth, rounded, glistening surface. The cut surface revealed large, yellow nodules, 5 to 6 cm. in diameter, with thick, interlacing bundles of dense, white, fibrous tissue. The uterus was small but the endometrium was velvety and thick and piled up into numerous sessile, polypoid masses. Microscopically the tumor was made up of interlacing, whorled bundles of plump, spindle-shaped cells interspersed with bands of dense, collagenous connective tissue. Scattered throughout the tumor were small nests of granulosa cells, many of which contained Call-Exner bodies (Fig. 5).

There was cystic hyperplasia of the endometrium.

The dense collagenous connective tissue bands did not take up the Sudan IV, whereas the plump, spindle-shaped cells showed numerous intra- and extracellular red droplets. The granulosa-cell nests also revealed a few scattered, extracellular fat droplets. These were fewer in number than those in the theca cells. Steroid substances, i.e., birefringent crystals

CASE 3.—Boston City Hospital; S47-5794. This 74-year-old white woman entered the hospital with a chief complaint of abdominal pain of two days' duration. She had had anorexia and constipation for the past four months with a diminishing caliber of her stools. She had ceased menstruating twenty years prior to admission and had had no vaginal bleeding since that time. She had noticed no weight loss. On physical examination there was left lower quadrant tenderness. Pelvic examination revealed a low, hard, fixed cervix. There was no discharge or bleeding from the cervix. The uterus was enlarged posteriorly and the size of a four months' pregnancy. An extrinsic mass was palpated on rectal examination. A barium enema was done and revealed that the entire sigmoid was displaced laterally and upward by a mass arising from the pelvis and probably encircling the sigmoid colon. The radiologist's impression was that there was no intrinsic large bowel tumor. A sigmoidoscopy was done and was negative. Laboratory tests were not remarkable except that the stools were guaiac positive.

Five days after admission a cervical biopsy was taken and revealed a chronic cervicitis. No tissue could be obtained from the endometrial cavity on dilatation and curettage. Two days later a laparotomy was performed. There was no free fluid in the peritoneal cavity. The liver, gallbladder, stomach, spleen, kidneys and large bowel were normal. Some of the loops of small bowel were thin and dilated and contained fluid. There were numerous adhesions in the pelvis involving loops of small bowel, the dome of the bladder, the fundus of the uterus, and both adnexae. There was a large mass of necrotic tissue lying in the pelvis. A portion of the mass, the "size of a baseball," was removed manually and this was followed by brisk bleeding. Several metastases to the serosa of the small bowel were noted. Because of the bleeding no further surgery was done.

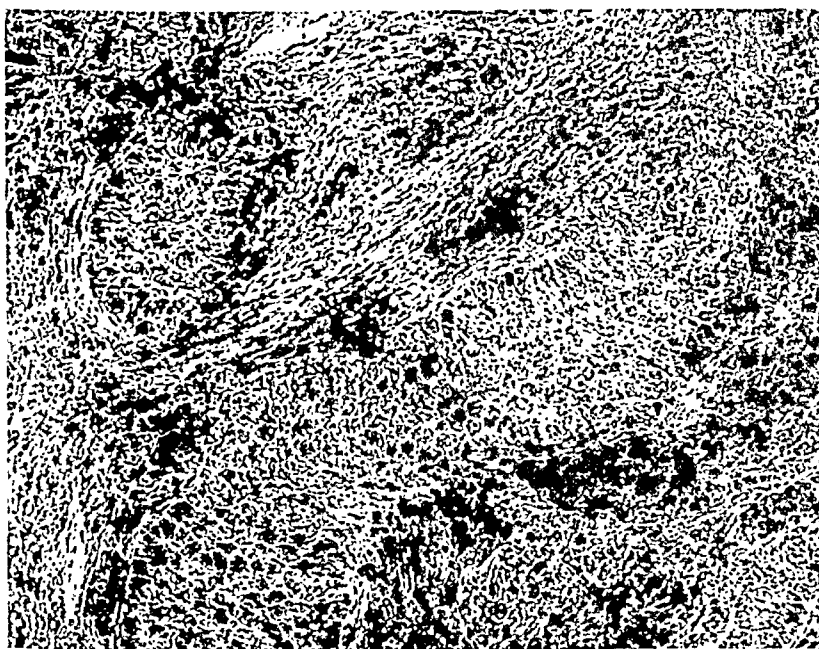


Fig. 3.—Photomicrograph of Sudan IV stain on granulosa-cell tumor of Case 2. Sudanophilic droplets absent in the cords of tumor cells but present in connective tissue cells and most abundant in those "theca-like" cells adjacent to the cords of tumor cells. ( $\times 160$ )

The urine contained no increase in estrogenic substances.

The patient did well postoperatively and was sent home for terminal care.

The pathologic specimen consisted of a soft, amorphous mass of tissue weighing 100 Gm. The tissue was gray to yellow with a few firm, white areas. There were scattered areas of necrosis and hemorrhage. Microscopically, the tumor consisted of sheets of cells with scant cytoplasm, poorly demarcated cell membranes, and round, irregular, vesicular nuclei

The pathologic specimen consisted of the uterus, both tubes, and ovaries. In the left ovary was a corpus luteum. In the right ovary there was a mass measuring 7 by 4 by 3.5 cm., which had a smooth, glistening, rounded surface and which on section revealed a whorled, yellow, solid mass of fibrous tissue. Microscopically it was a typical thecoma.

The endometrium was in the secretory phase of the cycle.



Fig. 6.—Photomicrograph of Sudan IV stain on thecoma of Case 6. Fat droplets are present intra- and extracellularly in bundles of plump, spindle-shaped theca cells but are absent in collagenous connective tissue bands and hyaline plaques. ( $\times 400$ )



Fig. 7.—Photomicrograph of frozen section of thecoma taken between crossed Nicol prisms. Birefringent crystals are present in theca cells. Birefringence of the fibrillar variety can be seen in the collagenous connective tissue bands. ( $\times 400$ )

Histochemical studies revealed a large number of sudanophilic droplets in the bands of spindle-shaped cells (Fig. 6), but none in the collagenous tissue or in the hyaline plaques. There were numerous birefringent crystals present (Fig. 7) and the tissue gave a positive reaction to sulfuric acid and the Schiff reagent.

exhibiting a faint, yellow-green fluorescence and reacting with sulfuric acid and Schiff's reagent were present in the plump theca cells but were absent in the collagenous connective tissue and were scant in the granulosa cell nests.

#### Thecoma With Foci of Luteinization

CASE 5.—Faulkner Hospital; S46-1514. This 32-year-old white woman entered the hospital with a chief complaint of a lump in the right lower quadrant. For the past five years she had had marked menstrual irregularities, consisting of periods of amenorrhea lasting as long as three months and followed by a scanty blood flow lasting one to two days. The two periods preceding entry had been characterized by an excessive flow for one day. On physical examination a plum-sized mass was palpable in the right lower quadrant. A dilatation and curettage and bilateral salpingo-oophorectomy were done.

The gross specimen consisted of two firm, irregular, gray and gray-pink masses. The larger was in the shape of three connected spheres which measured 16 by 8 by 5 cm. when stretched out. The smaller mass was ovoid and measured 7 by 5 by 3 cm. The tumors were covered with a dense, tough, glistening tissue. On section they revealed a dense, gray, whorled tissue with a few foci of soft, yellow tissue scattered throughout. Microscopically, the tumor consisted of whorls and bundles of plump, spindle-shaped cells. In several areas the cells were extremely large with a vacuolated to clear cytoplasm and with the nuclei located at one side of the cell.

The endometrium revealed a secretory response.

Sudanophilic droplets and reactive substances were present in the spindle-shaped theca cells but were seen in greatest amount in the luteinized theca cells. It is noteworthy that in this tumor there appeared to be a much larger amount of sudanophilic material than material giving the steroid reactions.

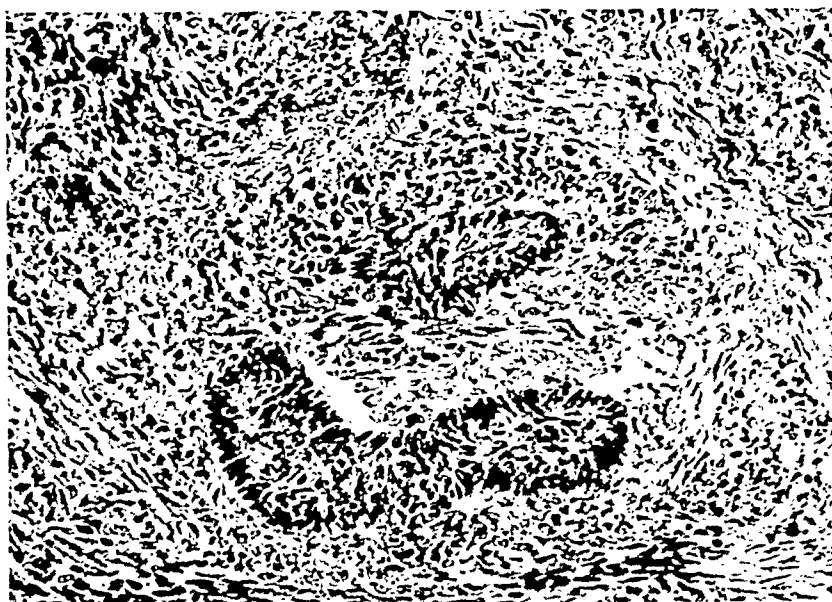


Fig. 5.—Photomicrograph of thecoma with granulosa-cell nests (Case 4). Phloxine-methylene blue stain. ( $\times 400$ )

CASE 6.—Massachusetts Tumor Diagnostic Service; S47-4911. This 36-year-old white woman entered with a chief complaint of pain in the epigastric region and dysmenorrhea for the past five to six months. She had not had dysmenorrhea prior to this time. In addition, she complained of an excessive flow at each of the previous five menstrual periods. The bleeding had lasted for seven to eight days, whereas it had never before lasted for longer than three days. Physical examination revealed a retroverted uterus and tenderness in both lower quadrants. A panhysterectomy was performed.



**CASE 10.**—Free Hospital for Women; S48-1775. This 75-year-old white woman entered the hospital with a chief complaint of "pain in the pelvis." There was no history of postmenopausal bleeding. Physical examination revealed a 4 by 3 inch mass in the left lower quadrant. A total hysterectomy and bilateral salpingo-oophorectomy were performed. The left ovary was replaced by a firm, solid tumor mass measuring 7 by 5.5 by 4.5 cm. The external surface was smooth, white, and glistening. On section it appeared white with small, scattered, yellow patches. The uterus contained several small leiomyomas.

Histologically, the ovarian tumor was made up of dense whorls of collagenous connective tissue with the characteristic pattern of an inactive thecoma. The endometrium was of the senile variety with a few scattered cystic glands, interpreted as the residuum of a previous hyperplasia. Histochemical examination revealed no steroid substances in this tumor.

**CASE 11.**—Free Hospital for Women; S47-5099. This 63-year-old white woman entered the hospital with a chief complaint of intermittent bleeding during the previous year and left lower quadrant pain for the previous three months. Endometrial curettings revealed adenocarcinoma of the uterine body. A hysterectomy and oophorectomy were done. In the left ovary was a firm, irregular mass measuring 5 by 4 by 3.5 cm. with a smooth, glistening surface. On section the cut surface was hard and had a whorled, white, fibrous appearance. Microscopically this tumor was made up of whorls of connective tissue with hyaline masses scattered throughout. Histologically it was a typical though inactive thecoma.

There were no sudanophilic droplets in this tumor and none of the tests for steroid substances was positive.

#### Fibromas

**CASE 12.**—Free Hospital for Women; S46-3716. This 19-year-old white woman entered the hospital with a chief complaint of left lower quadrant pain which had become worse in the last year. The pain was more severe at the onset of menstruation. She also complained of urgency and pressure on the bladder. The patient had also noticed that her breasts were sore at the time of menstruation. There was no history of amenorrhea, menorrhagia, or metrorrhagia. On physical examination a firm, suprapubic mass was palpated which displaced the uterus posteriorly. A laparotomy was performed and the mass removed from the left ovary. The patient continued to have regular menses and the breasts continued to be sore.

The pathologic specimen consisted of a tumor mass weighing 220 Gm. and measuring 7 by 8 by 7 cm., with a smooth, glistening, gray-white surface. On section the cut surface was firm, white, and presented a whorled, fibrous appearance. Microscopically, this tumor was made up of dense bands of collagenous connective-tissue cells. Neither plump, spindle-shaped cells nor hyaline masses were present. Curettage was done and revealed a menstrual endometrium.

There were no sudanophilic droplets or reactive steroid substances in this tumor.

**CASE 13.**—Salem Hospital; S47-455. This 65-year-old white woman entered the hospital with a chief complaint of pain in the right groin. She had had a normal menopause and there was no history of postmenopausal bleeding. A small tumor was palpated in the right ovary which was removed at a subsequent laparotomy.

The ovary contained a small, firm mass measuring 3 by 2 by 2 cm., with a rounded, smooth, glistening surface. On section it presented a firm, white, whorled, fibrous cut surface. Microscopically, it was composed of dense, collagenous connective tissue bundles and was characteristic of an ovarian fibroma.

There were no sudanophilic droplets or reactive steroid substance in this tumor.

#### Ovarian Carcinoma

**CASE 14.**—This 57-year-old white woman entered the hospital for the first time in March, 1940. Her chief complaint was menorrhagia. She had been bleeding continuously for the past five months. Her last regular period had been in October, 1939. Prior to that time

CASE 7.—Free Hospital for Women; S48-1483. This 65-year-old white married woman entered the hospital in January, 1948, with a chief complaint of vaginal bleeding. She had noted staining for the past six months and a heavy flow of bright red blood one week prior to entry. The last menstrual period had occurred fifteen years previously. A dilatation and curettage were performed which yielded distinctly hyperplastic endometrium. An incidental cervical polypectomy was also done. Following these procedures there was no further bleeding.

Because of the hyperplasia of the endometrium, which suggested the possibility of an ovarian tumor, she was brought back to the hospital in April, 1948, at which time a complete hysterectomy was done. The pathologic specimen consisted of the uterus, both tubes, and ovaries. The right ovary measured 1.5 by 2.5 by 3.5 cm. and was completely replaced by a nodular, yellow tumor with a whorled, gray-yellow cut surface and a 0.2 cm. cyst in its center. The left ovary was atrophic. Microscopically the tumor was a typical thecoma. Histochemical studies revealed a large quantity of reactive substances in the theca cells. The endometrium was hyperplastic with numerous large cystic glands.

CASE 8.—Free Hospital for Women; S47-4382. This 57-year-old white woman entered the hospital in 1947 with a prolapse of the uterus, an enterocele, and a cystocele. Her first admission had been in 1935, eight years after the delivery of her last child, when she entered with a chief complaint of menorrhagia with alternating periods of amenorrhea and periods of bleeding lasting up to six weeks. At that time a dilatation and curettage were done as well as a plastic repair of the prolapse, and a "sterilization dose" of radium was placed in the endometrial cavity. The endometrium at that time was atypical in appearance and was diagnosed endometrial dysplasia. Her menses ceased in 1935 but she had noted spotting in the several months prior to her admission in October, 1947. Physical examination revealed a mass in the pelvis as well as an enterocele, a cystocele, and a prolapse. The uterus, tubes, left ovary, and right ovarian tumor were removed and a plastic repair of the perineum was done.

The right ovarian mass weighed 620 Gm. and measured 14 by 10 by 8 cm. It had a smooth, rounded, white, glistening surface and on section revealed a solid, white, fibrous cut surface with streaks of yellow. Microscopically it was a typical thecoma with whorled bundles of spindle-shaped cells, among which were scattered the characteristic pink hyaline masses. The endometrium was of the senescent variety.

A few sudanophilic droplets and reactive steroid substances were present in small concentrations. The steroid material was confined to the plump, spindle-shaped cells and was absent in the collagenous connective tissue bundles and the hyaline masses.

#### Inactive Thecomas

CASE 9.—Free Hospital for Women; S48-1560. This 44-year-old white woman entered the hospital in August, 1947, with a chief complaint of intermenstrual bleeding and a more profuse flow with her periods. This abnormal bleeding was of three to four months' duration. Previously her menstrual cycle had been normal. Physical examination revealed a large, lacerated cervix attached to which was a small polyp. The latter was excised and a dilatation and curettage performed. Histologic examination revealed a benign cervical polyp and secretory endometrium.

The patient was discharged from the hospital and re-entered in April, 1948, complaining of two episodes of intermenstrual bleeding. A complete hysterectomy and left salpingo-oophorectomy were done. The uterus was not remarkable and the endometrium was of the secretory type with no evidence of hyperplasia. A solid tumor measuring 1.5 by 1.5 by 2.5 cm. was present in the left ovary at one pole. At the other pole was a hemorrhagic corpus luteum. The tumor was firm and on section revealed a white cut surface. Histologically, this tumor contained hyaline plaques and bands of dense collagenous tissue and was a typical thecoma of the inactive variety. There were no reactive substances anywhere in this tumor.

Sudan IV showed that the granulosa cells contained minute sudanophilic droplets in small numbers, but large amounts of this lipoid material were present in the surrounding "theca-like" spindle-shaped connective-tissue cells. This suggested to them that the granulosa cells had exerted an influence on the connective tissue immediately in contact with them in much the same way as granulosa cells of the developing Graafian follicle induce the immediately surrounding ovarian stroma to produce theca cells. The tumor cells of their second granulosa-cell tumor had intra- and extracellular sudanophilic droplets which were not birefringent, indicating, therefore, that there was no appreciable steroid material present. Their third tumor was a "theca-granulosa-cell tumor" similar to the fourth tumor in our group. Both of these tumors had plugs of granulosa cells containing small amounts of sudanophilic material. The adjacent stroma, furthermore, had a marked accumulation of fat which was birefringent in Greenblatt's case and gave all the reactions for steroid substances in our case. Greenblatt noted that the fat in the granulosa cells was not anisotropic.

These findings suggest that it is the "theca-cell" component of the granulosa-cell tumor which secretes the estrogenic hormone and not the granulosa cells. This is, therefore, similar to the situation that exists in the Graafian follicle.

Experimentally, the evidence is manifold that the granulosa cell does not produce estrogen and that theca cells do. Zondek and Aschheim<sup>14</sup> demonstrated that implantation of granulosa cells does not produce estrus in the castrate animal. Bell<sup>15</sup> castrated animals and grafted ovarian cortex from which follicles had been removed, leaving only theca cells. These animals developed a normal estrous cycle. The x-ray studies of Hüsey and Wallart<sup>16</sup> are more convincing. They irradiated the ovaries and produced follicular degeneration with a resultant proliferation of theca cells. The ovaries were converted into masses of theca cells that had definite hormonal activity. Melnick and Kanter<sup>17</sup> stated that the hormone in granulosa-cell tumors is perhaps derived from the adjacent mesenchyme and not from the tumor cells themselves. The histochemical studies herein reported tend to support this thesis.

Theca-like cells are probably present in most granulosa-cell tumors. Traut et al.<sup>18</sup> have demonstrated that the theca interna of the Graafian follicle contains a fine reticulum network which is absent in the granulosa layer. They applied the reticulum stain to granulosa-cell tumors and became convinced that in the well-differentiated or folliculomatous types of granulosa-cell tumor, as well as in the more undifferentiated types, representatives of both cellular layers of the Graafian follicle were present. In other words, many so-called granulosa-cell tumors contain considerable quantities of thecal elements.

There is but brief mention in the literature of non-functioning granulosa-cell tumors. Ewing<sup>19</sup> states that small, silent granulosa-cell tumors have been accidentally discovered at autopsy.

Hodgson et al.<sup>20</sup> in a study of sixty-two granulosa-cell tumors found four small tumors associated with atrophic endometrium—presumptive evidence that they were nonestrogenic. It is believed that our Case 3 is an example of a nonfunctioning granulosa-cell tumor. Like the other granulosa-cell tumors, its cells are devoid of reactive materials but unlike most of these tumors it contains no hormonally active thecal component. Urinary estrogens in this patient were not elevated and there was no history of postmenopausal bleeding.

The diagnosis in Case 3 can scarcely be in doubt. The tumor had several of the gross features of granulosa-cell tumor; other common sources of intra-

there had been no menstrual irregularities. A hysterectomy and left oophorectomy were done during this admission. The right ovary appeared normal at the time of operation. The left ovary contained numerous follicle cysts and the uterus was not remarkable except for a slight endometrial hyperplasia. She was discharged and remained well until April, 1945, when she re-entered with a complaint of right lower quadrant pain lasting for two months, which had suddenly become severe on the day of admission. A cyst was palpated in the right lower quadrant. A laparotomy was performed and a large mass of clotted blood and soft, yellow tumor tissue was found in the region of the right ovary. This mass was resected and measured 14 by 6 by 4 cm. Microscopically it consisted of sheets of cells with round to spindle-shaped nuclei with one or more prominent nucleoli. The cell membranes were indistinct and there was a very small amount of cytoplasm. There were numerous round, clear areas in between the tumor cells. In some areas the tissue had a reticulated appearance because of the great numbers of these clear spaces. Broad bands of fibrous tissue surrounded the sheets of tumor cells.

After the removal of the tumor the patient remained well until several months before her last entry in April, 1948, when she developed "discomfort in the lower abdomen." A mass was noted and it seemed to the patient to have increased in size. Physical examination revealed a palpable, cystic mass in the right side. At operation it was found to be adherent to the sigmoid colon and the bladder, and was removed with difficulty.

The pathologic specimen consisted of a soft, glistening, yellow mass of tissue measuring 8 by 10 by 6 cm. It had the appearance of fat and was lobulated. Microscopically, the tumor was identical with the portion of tumor removed in 1945.

A twenty-four-hour urine sample was collected and revealed no increased follicle-stimulating hormone or estrogen excretion.

Tests for steroid substances revealed large collections of reactive materials in the clear spaces in between tumor cells. In large areas of the tumor the cells were devoid of steroid substances, *but in others were found in the cytoplasm of the tumor cells.* There was also a small amount of reactive material in some of the connective-tissue cells of the interlacing fibrous bands.

In addition to these tumors, a Brenner tumor was available for study. The tumor gave no evidence of hormone production, which was to be expected, nor did it contain steroid substances on the histochemical examinations used in these investigations.

### Discussion

Because this is a small series of tumors, it would seem unwise to attempt to draw any final conclusions from it. In the following discussion those tentative conclusions which are suggested by the results are presented.

Although the granulosa cells of ovarian tumors, as well as those of normal ovaries, contain a few tiny intracytoplasmic sudanophilic droplets, they give none of the histochemical reactions which indicate the presence of ketosteroids. The tumor of Case 1 showed a "theca-cell" response of some of the connective tissue cells of the stroma, and these cells contained reactive substances. Unfortunately, no precise information was available which would indicate whether or not it was an estrogenically active tumor. The tumor of Case 2 was associated with a demonstrable increased estrogen production and followed this pattern.

This finding is in essential agreement with previous studies of a similar nature on estrogenic ovarian tumors. Schiller<sup>12</sup> found lipid mainly in the connective tissue bundles in between the granulosa cells. Greenblatt et al.<sup>13</sup> describe three granulosa-cell tumors, the first of which when stained with

The last tumor, Case 14, is not considered by the authors to belong in this series but is included because it was diagnosed a granulosa-cell tumor by several other pathologists. In our opinion it cannot be considered a granulosa-cell tumor from either the functional or the morphologic standpoint. The tumor, to the best of our knowledge, was nonestrogenic. There was no increased estrogen in the patient's urine and no elevation of follicle-stimulating hormone. No clinical evaluation of hormone production could be made since the uterus had been removed several years prior to the discovery of the tumor. Histologically, the tumor was made up of solid masses of elongated cells with prominent nucleoli and interlacing bands of connective tissue. There were no Call-Exner bodies and the cells were spindle-shaped rather than plump, rounded cells as one usually sees in most granulosa-cell tumors. The histochemical studies revealed reactive substances in the tumor cells and in the connective tissue cells as well. These probably represent deposits of cholesterol and cholesterol esters. Although the exact diagnosis of this tumor is in doubt, the authors consider it to be a solid ovarian carcinoma of undetermined type.

### Summary

Histochemical studies, designed to demonstrate the location of ketosteroids, were carried out on three granulosa-cell tumors, eight thecomas and two fibromas of the ovary. The functional state of each tumor was evaluated on the basis of the patient's history or the state of the endometrium, and in one case the estrogen concentration in the urine.

In general, the reactive materials were present in the theca cells of thecomas and in the theca-like cells of the granulosa-cell tumors. From these and other considerations it seems likely that the thecal component of granulosa-cell tumors, rather than the tumor cells themselves, is concerned in hormone production. One case of a nonestrogenic or "pure" granulosa-cell tumor is reported.

Steroid substances were not present in the collagenous connective tissue of thecomas nor in the two fibromas. It is concluded that histochemical studies are capable of differentiating active thecomas from inactive thecomas and fibromas.

We wish to express our appreciation to Dr. D. A. Nickerson of Salem Hospital, Dr. P. LeCompte of the Faulkner Hospital, and Drs. Olive Gates and S. Warren of the Tumor Diagnostic Service of the Massachusetts Department of Public Health for generously furnishing some of the specimens used in this study.

### Addendum

Since submitting this paper for publication, we have had a note by Boscott and co-workers<sup>24</sup> called to our attention. These authors tested three pure samples of desoxycorticosterone with Feulgen's plasmal reaction after treatment with cold mercuric chloride and found no evidence of oxidation of desoxycorticosterone to aldehyde by mercuric chloride. They conclude that this technique cannot be relied upon to demonstrate the cytological location of alpha hydroxyketones.

It should be noted, however, that the reactivity of the carbonyl linkage in different ketosteroids varies a great deal, and some do give this reaction (E. W. Dempsey, personal communication).

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abdominal carcinoma such as cervix, corpus uteri, bowel, etc., were made extremely unlikely by the various examinations mentioned previously; and finally, the tumor had the histologic characteristics of granulosa-cell tumor including Call-Exner bodies. The fact that it had metastasized locally to the peritoneum is not against the diagnosis, since Novak<sup>21</sup> reports that 28 per cent of granulosa cell tumors in his series were malignant.

Indeed, it would be quite strange if an occasional nonestrogenic granulosa-cell tumor did not present itself. There are few, if any, endocrine tissues elsewhere in the body which do not give rise to nonfunctioning tumors on occasion.

The presence of sudanophilic droplets which give the histochemical reactions of the steroid hormones in thecomas is in accordance with the findings of Melnick and Kanter<sup>17</sup> in two cases of thecoma. These authors found large quantities of sudanophilic material which was birefringent. Greenblatt et al.<sup>13</sup> reported that in thecomas the lipoids were abundant, where the connective tissue cells took on a plump, fusiform, epithelioid character, and that these lipoids were birefringent. In the present series of tumors the reactive materials were present in much larger amounts in the active thecomas than in either of the granulosa-cell tumors. It is interesting to note in this connection that Geist<sup>22</sup> states that the hormone content of the theca tumor in the one case examined was far greater in amount than that reported for granulosa-cell tumors.

In this study the thecomas divided themselves into two types—those that contained and those that did not contain reactive steroid substances. With one exception, Case 8, those thecomas which contained histochemically demonstrable steroids gave definite evidence of functional activity. Even in that case there was a history of irregular bleeding following an artificial menopause which might be evidence that the tumor was active in spite of the presence of a senescent endometrium. Parenthetically, it is interesting to speculate on the possible role the radiation may have played in producing this thecoma. Thecomas are easily produced in experimental animals by irradiation, and Traut and Butterworth<sup>23</sup> have mentioned a human case in which radiation may have resulted in the production of an estrogenic ovarian tumor.

At the Free Hospital for Women such a tumor followed the accidental exposure to x-rays in the case of a young woman who accompanied her mother while the latter was treated for carcinoma of the breast.

Conversely, the thecoma which was devoid of histochemically demonstrable steroids was likewise associated with no demonstrable increased estrogen secretion. This division of thecomas into two groups, an active and an inactive type, has been suggested by Traut and Butterworth.<sup>23</sup> It seems likely that a theca cell in a theca-cell tumor may go through a stage of active secretion, followed by an inactive phase, very much like the theca cell of the Graafian follicle which undergoes atresia. In Case 9 the history of menstrual irregularities several months prior to the time of removal of the tumor suggests that this thecoma had at one time been active but was inactive at the time of removal. It would seem that histochemical studies offer a good means for differentiating an active from an inactive thecoma.

The two cases of fibroma that were studied were free of steroid substances as was to be expected. The histochemical techniques, therefore, enable one to differentiate an active thecoma from a fibroma, but of course will not differentiate an inactive thecoma from a fibroma. The differentiation of the latter two tumors rests upon the morphologic appearance, but even this is often difficult.

## CARCINOMA OF THE OVARY\*

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THIS is a complete analysis of all cases of primary ovarian carcinoma treated at The Free Hospital for Women during a period of forty-three years, from 1903 through 1945. An attempt has been made to glean all possible information from this large group of cases which, through the years, has been carefully studied from clinical and pathological standpoints.

According to the hospital record room indices, 1,740 proliferative ovarian tumors† have been classified during this period of study. Of this number, 265 (15.2 per cent) have been considered malignant. Pemberton<sup>1</sup> analyzed 149 of these in 1938 and reported his results in 1940. A considerably different approach has been used in the present study, however, and 116 additional tumors, including other categories such as granulosa cell carcinoma, have been reviewed.

All cases were treated by surgery and many by x-ray as well. Operations were performed on both ward and private patients by various members of the staff. Therefore, this is actually a staff report.

### Method

The hospital records were searched for definite and borderline cases of primary ovarian carcinomas. Records of these cases were then carefully abstracted. All pathological reports were reviewed and the microscopic sections on every case re-examined, repeatedly in many cases. All borderline cases, as well as those that proved difficult of diagnosis, were re-evaluated by one of us (ATH). In the past, many of these difficult sections had been examined by Drs. Robert Meyer, Tracy Mallory, Shields Warren, S. Burt Wolbach, George Van S. Smith, Frank A. Pemberton, and others.

Admittedly, it has been difficult to determine microscopically whether some of these tumors were malignant or not. Some of our diagnoses would undoubtedly provoke agreement among some pathological authorities and disagreement among others. In some of the borderline cases, we have seen the host of such a tumor proceed through metastasis and on to death in a few months. Such cases frequently were used for comparative purposes in some of our decisions. Again, several tumors, notably those of the gross solid type, which defied every attempt at microscopic classification, were relegated to an undifferentiated group. Other authors would probably prefer to term these solid adenocarcinomas but we found a few partially cystic tumors which were just as undiagnosable as the solid types and elected to establish an undifferentiated group.

A classification was chosen which seemed to have practical significance from both clinical and pathological viewpoints. The primary classification was made on the basis of microscopic pathology. Further differentiation was made according to gross characteristics so as to be of value to the surgeon.

\*Read in part at the April, 1948, meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons at Boston, Mass.

†Cases of carcinoma were taken from the pathology files and the figures concerning the incidence of all ovarian tumors were taken from the record room files.

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Among a series of 1,268 dermoids, Meyer<sup>7</sup> found 1.7 per cent of them malignant. In this study, slightly less than 1 per cent proved to be so. No adequate figures have been found in the literature for the frequency of granulosa cell tumors or their malignant counterparts. We have found the incidence of granulosa cell tumors to be roughly 2 per cent of ovarian neoplasms, 30 per cent of which are malignant. Dockerty<sup>8</sup> states that clinical recurrences and metastases vary in different reports from 4.5 per cent to 33 per cent.

### Background of Patients

Of the total number of patients, 12.5 per cent gave a history of malignancy in their family. Montgomery,<sup>9</sup> in a recent article, found this figure to be 13.5 per cent. Ten per cent of our cases had a family history of tuberculosis while 3 per cent had had diabetes.

It may be noted that sixty (22.6 per cent) of our 265 cases had had gynecological operations in their past, fifty of these procedures having been for benign conditions and ten for malignancy of various types. Among the latter there were two breast carcinomas, two carcinomas of the cervix, one case of carcinoma of the endometrium and five cases of ovarian malignancy. The latter were composed of cases which either had been operated upon and considered hopeless or in which the other ovary had been removed years previously for malignancy. Ten of the cases had received radiation for benign bleeding or for some of the malignancies already mentioned.

### Age Distribution

Table II shows the number of cases occurring in each decade of life. As one might expect, for most malignancies, nearly 59 per cent of the patients were between the ages of 40 and 60 years at the time they appeared for treatment. The youngest patient was 23 and the oldest was 86. There were seven patients under the age of 30 while four were over 80. Patients with pseudomucinous carcinoma showed no significant age difference from those having the serous type although it is generally believed that pseudomucinous cysts arise after the menopause in only 10 per cent of women so afflicted. This would suggest that such cysts lie dormant for long periods of time before becoming malignant.

It seemed interesting to us that two of the three malignant dermoids occurred in the 70- to 80-year age group. It is generally thought that dysgerminomas occur in the younger age groups, but one of ours was in her fourth decade and the other in her sixth.

Premenopausal patients represented 39 per cent of the total cases while 61 per cent were in the postmenopausal period. It is interesting to note that 43 per cent of the premenopausal group were alive five years following treatment but that only 28 per cent of the postmenopausal patients lived that long. The factor of more advanced age in the latter group does not fully explain this difference in salvageability. Therefore, older patients apparently have more malignant tumors.

TABLE II. AGE DISTRIBUTION

AGE GROUP	NUMBER OF CASES
20-29	7
30-39	27
40-49	75
50-59	80
60-69	54
70-79	18
80-89	4
Total	265

Grading of the tumors, although often said to be unreliable, has been attempted according to established methods. Pemberton before us, Taylor and Greeley<sup>2</sup> and others have found such methods reliable. Our policy has been to consider the well-differentiated tumors as Grade I. The wildly anaplastic tumors with a profusion of mitoses and bizarre cells were denoted as Grade III. All the others gravitated to the Grade II group.

Short of FBI proceedings, the cases have been exhaustively followed through the years. Since 1942, 26 cases have received treatment. These cases have not had a five-year follow-up and this number has been deleted from any computation involving salvage figures.

The information thus gathered from many sources was then classified and recorded on punch-cards of our own design so that an infinite number of relationships could be established. Some of these relationships are shown on the tables to follow. For the sake of clarity and brevity, relationships of the minor subdivisions have been included only when considered especially significant or interesting.

### Incidence

Over a period of 45 years a total of 1,740 proliferative ovarian tumors have been encountered. In Table I the incidence of various benign types are compared to each other and to their malignant counterparts when possible.

TABLE I. INCIDENCE OF OVARIAN TUMORS

MICROSCOPIC TYPE	BENIGN TUMORS		MALIGNANT TUMORS		BENIGN AND MALIGNANT TUMORS	
	NUMBER	PER CENT OF TYPE	NUMBER	PER CENT OF TYPE	NUMBER	PER CENT OF ALL TYPES
Serous	347	68.4	160	31.6	507	29.1
Pseudomucinous	361	87.0	54	13.0	415	23.8
Unclassified cystadenoma	36	100.0			36	2.1
Dermoid cyst	313	99.0	3	1.0	316	18.2
Granulosa cell	26	70.3	11	29.7	37	2.1
Fibromas	359	100.0			359	20.6
Brenner	20	100.0			20	1.1
Miscellaneous benign*	13	100.0			13	.7
Undifferentiated carcinoma			24	100.0	24	1.4
Hypernephroma (Grawitz)			6	100.0	6	0.3
Endometriocarcinoma			3	100.0	3	0.2
Dysgerminoma			2	100.0	2	0.1
Carcinosarcoma			2	100.0	2	0.1
	1,475	84.8	265	15.2	1,740	100.0

\*Including leiomyoma, arrhenoblastoma, adenomyoma, and paraganglioma.

Dockerty<sup>3</sup> states that 15 per cent of all ovarian neoplasms are of the benign serous type and that the ratio of benign serous to benign pseudomucinous types is 3 to 4. Our incidence for benign serous type is 20 per cent and the ratio of serous to pseudomucinous is nearly 1 to 1. Novak<sup>4</sup> indicates this ratio to be about 1 to 1. Dockerty<sup>3</sup> also states that the number of benign pseudomucinous tumors constitutes from 20 to 30 per cent of all ovarian neoplasms. Our figure for this type approximates 21 per cent. In this series, dermoid cysts have occurred slightly less often than benign serous tumors.

When considering the incidence of malignant ovarian tumors, we found 265 of 1,740 neoplasms to be malignant. This is a frequency of 15.2 per cent which compares with Meyer's<sup>5</sup> findings of 14.9 per cent, Goldsmith's<sup>6</sup> 24 per cent, and Barzilai's<sup>7</sup> estimates of 21 per cent. Among these malignant tumors we obtained a ratio for serous to pseudomucinous types of 3 to 1. Barzilai's<sup>7</sup> figure for this ratio is 2½ to 1. About one-third of our serous tumors were found to be malignant while only 1 of 8 pseudomucinous tumors were so classified. This latter ratio is much greater than Novak's<sup>4</sup> experience of 1 in 20.

### Physical Signs

The relative incidence of the more important physical signs is shown in Table V. According to expectations, pelvic and abdominal masses occurred with great frequency. When the signs were distributed among the various tumor types of the primary classification, no statistically significant variation was found.

Ascites was tabulated whether it was found preoperatively or at operation. We found this sign in approximately 31 per cent of all cases and in 36 per cent of cases having a solid tumor. Geist<sup>12</sup> and Meigs<sup>14</sup> each quote a figure of 50 per cent for ascites in association with solid tumors. When we considered ascites as a prognostic factor, we discovered that 21 per cent of patients showing this sign were alive at five years; this is much lower than the over-all rate of 35 per cent.

TABLE V. PHYSICAL SIGNS

SIGN	NUMBER OF CASES	PER CENT
Pelvic mass	230	86.8
Abdominal mass	203	76.6
Ascites	82	30.9
Weight loss	75	28.3

### Pathology

The punch-card system has been extremely useful for correlating pathological attributes of various types of ovarian carcinomas with each other and with their clinical features. Microscopic types, gross types, grading and papillarity are discussed separately and comparatively.

Our primary break-down of cases is shown in Table VI. The usual microscopic designations of type were used with the exception of an undifferentiated group which is composed of those cases we could not honestly classify and the endometriocarcinomas. The endometriocarcinomas include those cases in which we felt sure the carcinoma had arisen in a pre-existing endometrioma. In this connection, Smith<sup>13</sup> estimated that 22 per cent of the better-differentiated ovarian carcinomas were either associated with, or related to, endometriosis.

TABLE VI. CLASSIFICATION

MICROSCOPIC TYPE	NUMBER OF CASES	PER CENT OF CASES
Serous cystadenocarcinoma	160	60.3
Pseudomucinous cystadenocarcinoma	54	20.3
Undifferentiated adenocarcinoma	24	9.1
Granulosa cell carcinoma	11	4.2
Malignant dermoid	3	1.1
Hypernephroma (Grawitz tumor)	6	2.3
Dysgerminoma	2	0.8
Endometriocarcinoma	3	1.1
Carcinosarcoma	2	0.8
Total	265	100.0

#### A. Primary Classification and Its Relationships.—

(1) *Bilateral Tumors:* The incidence of bilateral ovarian carcinomas, as determined at the first operation, is shown in Table VII. The total occurrence of 32 per cent seems low when compared with other series. Montgomery,<sup>9</sup> in a recent review of 87 cases, showed a 70 per cent bilaterality. This difference may be explained, in part, by a greater number of advanced cases in his series.

Pseudomucinous carcinomas are least likely to be bilateral (15 per cent) and the undifferentiated types most likely to be so (50 per cent) while the serous group occupies an intermediate position with 37 per cent.

Marital Status

Married patients comprised 81.6 per cent of the total and 31.5 per cent of them had not had any term pregnancies. Wharton<sup>10</sup> states that about 10 per cent of married couples are sterile. Other estimates run around 15 per cent. Dockerty,<sup>3</sup> in his extensive review, indicates that 40 per cent of women with ovarian cancer are sterile. Thus, our figures tend to agree that patients suffering from cancer of the ovary are less fertile as a group. There was, however, no significant deviation among the various tumor types with respect to this infertility.

Symptomatology

Enumeration and relative frequency of various symptoms are shown in Table III. None of these symptoms are very specific. As in most other studies of ovarian cancer, low abdominal pain and abdominal enlargement are the preponderating symptoms. When the symptom of pain was plotted against prognosis, it was found that cases with this complaint had neither better nor worse five-year salvage figures.

TABLE III. SYMPTOMS

SYMPTOM	NUMBER OF CASES	PER CENT OF CASES
Low abdominal pain	143	53.9
Abdominal enlargement	142	53.5
Gastrointestinal complaints	57	21.5
Genitourinary complaints	53	20.0
Abnormal vaginal bleeding	49	18.5
Pelvic pressure	46	17.4
Backache	36	13.5

The figure of 18.5 per cent for abnormal vaginal bleeding has been corrected for causes probably unrelated to the ovarian cancer such as endometrial hyperplasia, fibroids, and primary associated endometrial carcinoma. Meigs<sup>11</sup> reported 30 per cent of ovarian malignancies as having abnormal bleeding but it is not stated whether his figures were corrected in this manner.

Of the 49 cases with vaginal bleeding (excluding the probable unrelated causes enumerated above), thirteen were most likely due to the occurrence of endometrial metastasis. This leaves a balance of 37 cases wherein the cause of bleeding is unknown but may possibly be explained on the basis of generally hyperactive ovarian stroma.

The incidence of abnormal vaginal bleeding was the same for both the premenopausal and postmenopausal groups.

When the duration of symptoms was plotted against five-year salvage (Table IV), it was found that those cases having symptoms longer than six months had a slightly better prognosis. Again, when the duration of symptoms was compared with the number of cases presenting metastasis (Table IV), it was seen that the patients having symptoms of less than six months had a considerably higher metastatic rate. At first glance it would seem that the reverse of these situations should be true, i.e., the longer the patient played host to a tumor, the greater the chance for metastasis to develop and the poorer the prognosis would be. We explain this paradox by postulating that cases with shorter duration of symptoms had a more fulminating type of lesion.

TABLE IV. DURATION OF SYMPTOMS VS. PROGNOSIS AND METASTASIS

DURATION	NUMBER OF CASES	FIVE-YEAR SALVAGE		METASTASES	
		NUMBER	PER CENT	NUMBER	PER CENT
Three months	69	23	33.3	41	59.4
Six months	57	20	35.1	33	57.9
Six months plus	100	37	37.0	47	47.0
Total	226*	80	35.4	121	53.5

\*The duration of symptoms was not clear in all cases. In other cases a five-year follow-up was not available.

It is evident that the undifferentiated tumors are the most malignant, for 96 per cent of them fall into Grades II and III with 78 per cent in the latter grade. The pseudomucinous group, on the other hand, is the least malignant, as 94 per cent of it is relegated to the Grade I and Grade II classifications. The serous carcinomas occupy a position intermediate to the above groups with 73 per cent of their number falling into Grades II and III. Thus an order of malignancy can be established for the main tumor types. (The granulosa cell carcinomas were not graded and the miscellaneous types were too few in number to be of any statistical significance.)

TABLE IX. RELATION OF MICROSCOPIC CLASSIFICATION TO GRADING

CLASSIFICATION	NUMBER OF CASES	PER CENT OF CASES		
		GRADE I	GRADE II	GRADE III
Serous	156	27	39	34
Pseudomucinous	52	46	48	6
Undifferentiated	23	4	18	78
Malignant dermoid	2	50	0	50
Hypernephroma	3	33	33	33
Carcinosarcoma	2	0	0	100
Endometriocarcinoma	1	0	0	100
	239*	29	38	33

\*In some categories, notably granulosa cell carcinoma, grading was not done in all cases. A sufficient number were graded, however, to obtain a fair sampling of morphologic variants.

(5) *Metastasis*: It appears that tumors showing metastasis at operation are more malignant than those without. This belief arises from the fact that only 21 per cent of patients having metastasis lived for five years while the over-all salvage at five years is 35 per cent.

TABLE X. METASTASES

CLASSIFICATION	TOTAL CASES	CASES WITH METASTASES		LOCATION OF METASTASES		
		NUMBER	PER CENT	PER CENT OF METASTASES IN		
				PELVIS	ABDOMEN	UTERUS
Serous	160	89	56	87	64	8
Pseudomucinous	54	21	40	57	71	38
Undifferentiated	24	17	71	94	77	18
Granulosa cell carcinoma	11	5	45	60	60	0
Malignant dermoid	3	1	33	100	0	0
Hypernephroma	6	1	17	100	0	100
Endometriocarcinoma	3	0	0	0	0	0
Dysgerminoma	2	2	100	100	50	0
Carcinosarcoma	2	1	50	100	100	0
	265	137	52	82	66	14
Total pelvic metastases		113	(43 per cent of all cases)			
Total abdominal metastases		90	(34 per cent of all cases)			
Total uterine metastases		19	(7 per cent of all cases)			

Metastasis had occurred in 52 per cent of the 265 cases at the time of operation (Table X). The pelvic cavity was the most frequent site of metastasis (82 per cent), but 66 per cent of the metastases were found in the abdominal cavity and 14 per cent in the uterus, chiefly in the endometrium. The overlap in percentages is accounted for by the fact that many cases had both abdominal and pelvic metastases while several had them in the endometrium as well. When the frequencies of metastatic site are compared to the total number of cases (265), it is found that 43 per cent of the cases had pelvic metastases, 34 per cent had metastases in the abdominal cavity, and 7.2 per cent in the uterus.

Serous carcinomas tended more to pelvic metastasis, while pseudomucinous types tended more to the abdominal cavity. Pseudomucinous tumors metastasized to the endometrium in a surprising number of instances, namely, in 8 of 21 cases.

TABLE VII. BILATERAL TUMORS

CLASSIFICATION	NUMBER OF CASES	PER CENT OF CASES WITH BILATERAL TUMORS
Serous	160	36.9
Pseudomucinous	54	14.8
Undifferentiated	24	50.0
Granulosa cell carcinoma	11	27.3
Malignant dermoid	3	0.
Hypernephroma	6	16.7
Miscellaneous*	7	42.8
Total	265	32.1

\*See Table VI for identity of these tumors.

(2) *Size of Tumors:* The size of the tumor (or of the ovary containing the tumor) was recorded in 255 cases. Size was classified as small (up to 5 cm.), medium (5 to 15 cm.), and large (15 cm. or more). Thus it may be seen from Table VIII that 60 per cent of all the tumors fell into the maximum-sized category, while only 5 per cent were under 5 cm. The majority of tumors possess a fairly large mass, which fact may be of considerable clinical importance.

When the primary break-down is used for comparative purposes, the pseudomucinous group contains a huge majority (81 per cent) of large tumors while the serous group has a smaller majority (56 per cent) of maximum-sized tumors. The undifferentiated tumors average somewhat less by comparison. The granulosa cell carcinomas are preponderantly medium-sized tumors, which is consistent with the smaller size of their benign counterparts.

TABLE VIII. SIZE OF TUMORS

CLASSIFICATION	PER CENT OF CASES WITH		
	SMALL TUMORS	MEDIUM TUMORS	LARGE TUMORS
Serous	3.9	39.9	56.2
Pseudomucinous	1.9	17.0	81.1
Undifferentiated	13.0	39.1	47.9
Granulosa cell carcinoma	18.1	45.5	36.4
Malignant dermoid	0.0	0.0	100.0
Miscellaneous	8.3	41.7	50.0
	5.1	34.9	60.0

(3) *Contents of Cysts:* The type of fluid present in the cystic portions of the tumors was described in 156 cases. There were a considerable number of cysts which contained blood in addition to other fluids. This was probably due to operative trauma in many cases but may represent a close relationship to endometriosis or even indicate that the malignant process arose in an endometrioma.

A majority of the serous cysts contained serous fluid, but 28 per cent contained pseudomucinous material as well. Although 83 per cent of the pseudomucinous cysts showed fluid characteristic of their type, it is notable that 26 per cent of them contained serous fluid also.

Because of the presence of more than one type of fluid in a cystic tumor, it must be concluded that a reliable diagnosis of histologic type cannot invariably be made upon consideration of the fluid alone.

(4) *Grading:* Table IX shows the relationship of microscopic type to grading in 239 cases. Grade I tumors comprised 29 per cent of the total while Grade II and Grade III were 38 per cent and 33 per cent, respectively. When the more malignant tumors (Grade II and Grade III) were considered, a percentage of 71 was obtained. This figure agrees rather closely with Montgomery's whose Grade II and Grade III cases totaled 73.5 per cent.

TABLE XIV. RELATION OF GROSS TYPE TO METASTASIS

GROSS TYPE	NUMBER OF CASES	METASTASES	
		NUMBER	PER CENT
Cystic	80	25	31.2
Semisolid	138	81	58.7
Solid	35	30	85.7

TABLE XV. RELATION OF GROSS TYPE TO PROGNOSIS

GROSS TYPE	NUMBER OF CASES	ALIVE AT 5 YEARS	
		NUMBER	PER CENT
Cystic	74	43	58.1
Semisolid	130	38	29.2
Solid	28	5	17.8

### Significance of Papillae

It is well known that a large number of proliferative ovarian cysts, both benign and malignant, contain papillae. We have attempted to determine whether tumors presenting gross papillae are more or less malignant than those without such protrusions by comparing papillary tumors with gross type, grading, and prognosis. Further breakdown was made by dividing papillae into inverting and everting types.

Apart from the fact that 74 per cent of the malignant tumors showed papillae, of both inverting and everting types, no conclusions could be drawn as to their significance with regard to degree of malignancy.

### Grading

Grading has been used in this study as a factor in determining the degree of malignancy. In Tables XVI, XVII, and XVIII, we have used the factors of metastasis, prognosis, and radiation response as a check on the reliability of the grading procedure.

In proceeding from Grade I to Grade III, it may be noted that the metastatic rate rises from 31 per cent to 74 per cent. An inverse relation exists for five-year salvage: 65 per cent for Grade I tumors down to 7 per cent for Grade III.

TABLE XVI. RELATION OF GRADING TO METASTASIS

GRADING	NUMBER OF CASES	METASTASES	
		NUMBER	PER CENT
Grade I	71	22	31.0
Grade II	92	50	54.3
Grade III	82	61	74.4
	245	133	54.2

TABLE XVII. RELATION OF GRADING TO PROGNOSIS

GRADING	NUMBER OF CASES	FIVE-YEAR SALVAGE	
		NUMBER	PER CENT
Grade I	63	41	65.1
Grade II	91	34	37.4
Grade III	69	5	7.2
	223	80	35.9

In general, the more anaplastic a tumor, the greater the susceptibility to radiation. This is rather well borne out in Table XVIII where the percentage of improvement with added x-ray advances from 31 per cent for Grade I tumors to 85 per cent for Grade III tumors. Incidentally, it may be seen from this same chart that x-ray added to surgery improves the five-year salvage by 69 per cent.

If it can be assumed that metastasis is an indication of greater malignancy of a tumor type, it follows that the undifferentiated group is the most malignant since 71 per cent of its number metastasized. Next in order are: serous, 56 per cent; granulosa cell carcinoma, 45 per cent; and pseudomucinous, 40 per cent. This is the same order of malignancy that was obtained by grading.

(6) *Salvage Rates (Prognosis)*: Table XI gives the five-year salvage rates for all cases in our primary classification (26 cases had not been followed long enough). There is close agreement between prognosis and the order of malignancy previously established by grading and metastasis. The exception to this conclusion is the granulosa cell group, none of which was alive at the end of five years.

TABLE XI. COMPARISON OF SALVAGE RATES BY HISTOLOGICAL CLASSIFICATION

CLASSIFICATION	NUMBER OF CASES	ALIVE AT 5 YEARS	
		NUMBER	PER CENT
Serous	143	51	35.7
Pseudomucinous	51	24	47.1
Undifferentiated	22	4	18.2
Granulosa cell carcinoma	10	0	.0
Hypernephroma	4	1	25.0
Malignant dermoid	2	0	.0
Dysgerminoma	2	0	.0
Endometriocarcinoma	3	3	100.0
Carcinosarcoma	2	0	.0
	239	83	34.7

### Gross Pathology and Its Relationships

All tumors were divided into a gross classification of (a) cystic, (b) semi-solid (partly cystic tumors with solid areas of at least 2 cm. in diameter), and (c) solid. The latter group was predominantly solid although a few had small areas of cystic degeneration. The incidence of these gross types is shown in Table XII where it is seen that a large percentage of the pseudomucinous tumors are grossly cystic and the undifferentiated tumors are preponderantly of the solid variety. Here again, the serous and granulosa cell types, although showing a large percentage of semisolid and solid tumors, fall into an intermediate position. It is clinically important to note that 69 per cent of ovarian carcinomas contain solid areas of two centimeters or more.

TABLE XII. GROSS CLASSIFICATION

MICROSCOPIC TYPE	GROSS TYPE PER CENT		
	CYSTIC	SEMI-SOLID	SOLID
Serous	26	68	8
Pseudomucinous	61	35	4
Undifferentiated	4	22	74
Granulosa cell carcinoma	20	70	10
Miscellaneous	22	64	14
	31	55	14

By determining the relative position of these gross types with regard to grading (Table XIII), metastasis (Table XIV), and prognosis (Table XV), we have attempted to prove that the completely cystic tumors are the least malignant and the semi-solid and solid types are progressively more so.

TABLE XIII. RELATION OF GROSS TYPE TO GRADING

GROSS TYPE	GRADE I PER CENT	GRADE II PER CENT	GRADE III PER CENT
Cystic	55	36	9
Semisolid	21	42	37
Solid	0	27	73



## Results of Treatment

Only the 239 cases which were followed for at least five years are considered in this section. All of the cases were operated upon by various members of the staff through the years. Although, at the time of this study, it was impossible to ascertain the intentions of the various operators, it seems to have been the policy to remove as much of the growth and as many of the pelvic organs as possible, at times seemingly without regard for the apparent hopelessness of the situation. This fact may have been of importance in the five-year salvage figures which are somewhat above the average quoted by most authors.

For a time it was considered wise to perform an excision of the omentum routinely but an analysis of these cases showed no improvement in salvage figures. Before the advent of x-ray therapy, the use of lead had some vogue in the post-operative treatment of a number of these cases. It has been impossible to attribute any favorable effect on prognosis to this method of treatment. Radium was used on a few patients with similarly negligible results.

Since 1930 many cases have been treated with deep x-ray therapy in addition to the usual surgical procedures. Eighty-five such cases are reported at this time. The dose has varied from 3,000 to 9,000 r. and some of the patients did not complete the recommended number of treatments. There is no discernible reason why some patients were selected for this form of therapy. However, at the present time it is a general rule that all patients with ovarian carcinoma receive x-radiation in addition to surgery.

Table XX shows the disposition of all patients at the end of five years. It should be noted that our over-all five-year salvage figure of 35 per cent has not been corrected for postoperative deaths, deaths from intercurrent disease, or for those patients who became untraceable before five years had elapsed. In other words, all patients dead or untraceable at the end of five years were counted as cancer deaths. On the other hand, it was known that a few of the patients alive at the end of five years still had incurable cancer.

TABLE XX. COMPARISON OF SALVAGE RATES BY HISTOLOGICAL CLASSIFICATION

CLASSIFICATION	NUMBER OF CASES	POST-OPERATIVE DEATHS	DEAD OF OTHER DISEASES	DEAD OF CARCINOMA	UN-TRACED	ALIVE AT FIVE YEARS	
						NUMBER	PER CENT
Serous	143	10	6	62	14	51	35.7
Pseudomucinous	51	1	1	21	4	24	47.1
Undifferentiated	22	3	1	13	1	4	18.2
Granulosa cell	10	0	1	7	2	0	.0
Hypernephroma	4	0	0	2	1	1	25.0
Dermoid	2	0	1	1	0	0	.0
Dysgerminoma	2	0	0	2	0	0	.0
Endometriocarcinoma	3	0	0	0	0	3	100.0
Carcinosarcoma	2	0	0	2	0	0	.0
	239	14	10	110	22	83	34.7

The operative mortality rate was 5.9 per cent (14 deaths occurring within 40 days from the time of operation). The fact that ten of these deaths occurred in the decade 1933 to 1942 does not correlate very well with the generally improved surgery of that period. Four per cent of the patients died of intercurrent disease during the first five-year follow-up period while 9 per cent were lost. At the end of these first five years, 46 per cent of the total patients were dead from progressive or recurrent cancer, most of these dying within two years of operation. This left 83 living patients or an over-all five-year salvage figure of 35 per cent. The latter figure is higher than Meig's<sup>11</sup> 15 per cent, Mont-

TABLE XVIII. RELATION OF GRADING TO RADIATION RESPONSE

GRADING	PER CENT FIVE-YEAR SALVAGE		PER CENT IMPROVEMENT
	SURGERY ALONE	SURGERY AND X-RAY	
Grade I	58	76	31
Grade II	32	47	47
Grade III	2	19	850

### Associated Pathology

Table XIX shows the incidence of the accompanying types of pathology. All this pathology was located in the pelvis with the exception of five cases of colonic carcinoma, some of which were partly within the pelvis, and two cases of breast cancer. The percentage (11 per cent) of associated benign ovarian tumor may seem surprising, although Smith<sup>13</sup> noted that 23 per cent of all proliferative ovarian tumors showed two or more types of primary new growth. This multicentric tendency may also account for the occurrence of three cases of multiple primary carcinoma of the ovary in our series.

TABLE XIX. ASSOCIATED PATHOLOGY

	NUMBER OF CASES	PER CENT OF CASES
Other primary cancers	21	7.9
Benign ovarian tumors	28	10.6
Fibroids	90	34.0
Pelvic inflammation	71	26.8
Endometrial hyperplasia	34	12.8
Endometriosis and adenomyosis	31	11.7

The occurrence rate of associated uterine fibroids (34 per cent) is somewhat higher than the attack rate for this type of tumor in noncancerous women. Novak<sup>4</sup> and Wharton,<sup>10</sup> respectively, state this rate to be 20 per cent and 26 per cent in women over age 30.

The cases having chronic salpingitis were not divided into primary and secondary types of inflammation so that little can be deduced from them as possible etiologic agents.

Endometrial hyperplasia occurred in 13 per cent of our cases. This figure may seem rather high for a female population of this age group, but it must be realized that one-third of these hyperplasias occurred in cases of granulosa cell carcinoma, all of which showed this condition.

Endometriosis and adenomyosis have been grouped together and show an incidence of 11.7 per cent. A large proportion of these cases had endometriosis of the external type and, in 20 cases (7.6 per cent of our entire series), this was located in an ovary on the involved or opposite side.

### Multiple Primary Carcinoma

Twenty-one (8.3 per cent) of the 265 cases herein presented had multiple primary cancer. Two of these cases had three separate primary sources of the disease, one showing adenocarcinoma of the endometrium and of the colon in addition to the ovarian carcinoma. Another case presented a separate adenocarcinoma of the endometrium and a small but definite sarcoma located but a few millimeters from the ovarian carcinoma.

In eleven of the twenty-one cases, the other primary malignancy arose in the endometrium. There were three cases in which the different cancer type was located in the same or other ovary. The remainder of the multiple primary foci were in the colon (five instances), cervix (two instances), and breast (two cases). In some instances the additional neoplasms had existed prior to the discovery of the ovarian lesion while some were discovered at follow-up operations.

Table XXIII compares the results of various operations, with and without x-ray. The exploratory type of operation naturally carried the poorest prognosis for these patients had such extensive disease and metastasis as to preclude any attempt at removal. This same hopeless situation often prevailed in cases where oophorectomy alone was done. In all but a few cases where hysterectomy was performed, bilateral oophorectomy was also accomplished. There is very little statistical difference between the results from the supravaginal and those from the complete type of hysterectomy. The relatively small number of the latter is but an indication of the more recent trend toward complete hysterectomy.

### Summary and Conclusions

1. During a period of 43 years, 1,740 proliferative ovarian tumors were found at the Free Hospital for Women. Of these tumors, 265 were malignant.

2. The incidence of benign and malignant types found in this clinic compares favorably with that of several authorities.

3. History of malignancy in the family occurred in 12.5 per cent of the patients.

4. In their past histories, 22.6 per cent of the patients had had gynecological operations, 9 of which were for various other malignancies.

5. The ages of the patients were distributed according to the usual expectancy for cancer; 59 per cent of them were between the ages of 40 and 60. The prognosis for premenopausal patients is much better than for postmenopausal, despite correction for the age factor.

6. Sterility occurred in 31.5 per cent of the patients.

7. The symptoms of ovarian carcinoma are not very specific. Lower abdominal pain and abdominal enlargement each occurred in 54 per cent of the cases.

8. Patients with short duration of symptoms (under six months) had a less favorable prognosis and a considerably higher metastatic rate.

9. Pelvic and abdominal masses occurred with great frequency. Ascites was present in 31 per cent of all cases and in 36 per cent of cases having a solid tumor. Ascites connotes a poorer prognosis.

10. Ovarian carcinoma occurred bilaterally in 32 per cent of the cases. Pseudomucinous carcinomas were bilateral in 15 per cent and the serous type in 37 per cent of the cases.

11. Only 5 per cent of the tumors measured 5 cm. or less, and 60 per cent of them were 15 cm. or more in diameter. Pseudomucinous tumors were large in 81 per cent of the patients.

12. The cyst contents showed considerable admixture of various types of fluid, and, therefore, a completely reliable diagnosis cannot be made on the type of fluid alone.

13. The order of malignancy for the various tumor types, as judged by grading, rate of metastasis, and salvage rates, is granulosa tumor, undifferentiated tumors, serous and pseudomucinous carcinoma, the latter being least malignant.

14. Metastasis occurred in 52 per cent of all cases. Patients with metastasis had a poorer prognosis. Uterine metastasis had occurred in 7.3 per cent of the cases.

gomery's<sup>9</sup> 20.5 per cent, and an early series of Taylor's,<sup>16</sup> 15 per cent. Taylor<sup>2</sup> reported a later series, however, which included patients treated with x-ray, in which his over-all salvage for five years was 35 per cent.

Table XXI shows the long-time follow-up of the 239 patients, giving the per cent alive at the end of each successive five-year interval. Age and inter-current disease took the largest toll of these patients after their first five years of follow-up although definite recurrences were noted after the following intervals: twenty years (2 cases), seventeen years, nine years (2 cases), eight and one-half years, and five years.

TABLE XXI. LONG-RANGE FOLLOW-UP OF ALL PATIENTS

PERIOD	NUMBER OF CASES	PER CENT ALIVE AT FIVE-YEAR INTERVALS					
		5 YEARS	10 YEARS	15 YEARS	20 YEARS	25 YEARS	30 YEARS
1903-1912	18	28	22	22	6	6	0
1913-1917	17	18	6	6	6	6	6
1918-1922	18	33	33	22	11	0	
1923-1927	37	38	27	16	6		
1928-1932	40	30	20	8			
1933-1937	53	42	30				
1938-1942	56	38					
	239	35	25	14	7	4	3

Table XXII compares the results from surgery alone with those from surgery plus x-ray over a fifteen-year follow-up span. It is interesting that the results from added x-ray show considerable improvement in the five- and ten-year salvage rates but that at fifteen years the figures are identical. This tends to confirm observations by Pemberton<sup>1</sup> and others that radiation therapy increases longevity and comfort of the patient but does not necessarily cure the disease. The results from surgery alone appear more unfavorable than they really are when compared to those cases receiving x-ray since all the postoperative deaths are absorbed in the former group. When a correction factor for this is introduced, however, the results of the cases x-rayed are still 12 percentage points better than with surgery alone.

TABLE XXII. COMPARISON OF SURGERY TO SURGERY AND X-RAY

INTERVAL	PER CENT ALIVE AT FIVE YEARS		
	SURGERY	SURGERY AND X-RAY	COMBINED
5 years	29	46	35
10 years	20	36	25
15 years	14	14	14

TABLE XXIII. COMPARATIVE RESULTS OF VARIOUS OPERATIVE PROCEDURES

OPERATION	SURGERY ALONE		SURGERY AND X-RAY		COMBINED TREATMENT	
	NUMBER	PER CENT ALIVE AT 5 YEARS	NUMBER	PER CENT ALIVE AT 5 YEARS	NUMBER	PER CENT ALIVE AT 5 YEARS
Exploratory and/or biopsy	12	8.3	6	0.0	18	5.5
Oophorectomy	38	13.2	15	33.3	53	19.0
Supravaginal hysterectomy and oophorectomy	89	38.2	47	48.9	136	42.0
Complete hysterectomy and oophorectomy	15	26.6	17	64.7	32	47.0
	154	29.0	85	45.9	239	35.0

# THE HISTOLOGIC APPEARANCE OF THE ENDOCERVIX DURING THE MENSTRUAL CYCLE\*

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SINCE the work of Hitschmann and Adler, it has been established beyond dispute that the human endometrium undergoes characteristic cyclic changes during the ovulatory menstrual cycle. The study done by Novak and Everett<sup>1</sup> showed definitely that cyclic histologic variations also occur in the endosalpinx. The investigation made by Diereks<sup>2</sup> demonstrated certain cyclic changes in the vaginal mucosa. In regard to the latter, however, subsequent studies have yielded somewhat conflicting results (note the reports of Geist,<sup>3</sup> Traut, Bloch and Kuder,<sup>4</sup> and Zondek and Friedmann<sup>5</sup>). Zondek and Friedmann, for example, failed to find in the vaginal mucous membrane any changes comparable to those found in the endometrium. Their report maintained that in different parts of the vaginal mucosa varying microscopic pictures prevailed. This may be due to the nature of the embryologic development of the vagina, only part of which is supposed to be Müllerian in origin. In keeping with these genital tract findings, one would naturally be led to believe that the cervix, which, like the uterus and tubes, is entirely of Müllerian origin, must also undergo cyclic variations in its mucous membrane. The investigations of Wollner<sup>6, 7, 8</sup> and the work of Sjövall<sup>9</sup> indicated that such variations do exist. Although both Wollner and Sjövall found cyclic changes in the human endocervix, their descriptions, and consequently, their interpretations of those changes were entirely different.

This study was made to determine the nature of the histologic appearance of the endocervix during the menstrual cycle. Does the endocervix undergo cyclic histologic changes? If so, can these changes be correlated with those found in the endometrium?

## Procedure

The subjects for study were women in the reproductive period of life, normal physically and gynecologically, with histories of normal menstrual periods. They were selected from groups of postpartum patients who were not lactating, and who reported to the outpatient department immediately after the end of their first menstrual periods. These patients were examined, and those who had a vaginal discharge or cervical infection were discarded from the study. The patients who were retained for study returned at specified dates during subsequent menstrual cycles, at which times specimens of endometrium and endocervix were obtained concomitantly. For procuring

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15. Ovarian carcinomas contained solid areas of at least 2 cm. in diameter in 69 per cent of the cases. Cystic, semisolid and solid tumor types were progressively more malignant, in that order, as judged by grading, metastasis, and prognosis.

16. Apart from the fact that 74 per cent of the malignant tumors showed inverting and everting papillae, no conclusions could be made as to their significance with regard to degree of malignancy.

17. Grading is a reliable and important procedure when checked against the factors of metastasis, prognosis, and radiation response.

18. In 8.3 per cent of the cases, more than one type of primary cancer was found at the time of operation or later in the follow-up. About one-half of these cancers were located in the endometrium.

19. The combined results of treatment of all types produced 35 per cent salvage at the end of their first five years; 46 per cent died of cancer, 4 per cent died of other diseases, 9 per cent were lost, and 5.9 per cent died as a result of the operation.

20. The results from surgery alone at the end of five-, ten-, and fifteen-year intervals were, respectively, 29 per cent, 20 per cent, and 14 per cent. The results from surgery with the addition of x-ray for the same intervals were 46 per cent, 36 per cent, and 14 per cent.

21. Recurrences have occurred as long as twenty years following operation. Seven recurrences were noted after five years.

22. The results from any operation other than hysterectomy and bilateral oophorectomy were negligible. The complete hysterectomy seemed to have a slight advantage over the supravaginal type.

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of a gland and not in the rest of it. The amount of secretion from the gland cells varied, but some secretion could be seen under high magnification in most lumina. The extent of secretion was in no way related to the phase of the menstrual cycle, to the presence or absence of papillary excrescences, or to the position of the nuclei in relationship to the basement membrane. There was no evidence of denudation of the lining membrane during menstruation. The stroma consisted of dense connective tissue, among the fibers of which could be seen an occasional small blood vessel. The cell nuclei were usually quite large, mainly oval or spindle in shape, occasionally round, depending upon whether seen flatly or in profile. No evidence of congestion, edema, or devitalization of tissue was found. Mitotic figures could not be observed in the nuclei of the stromal or epithelial cells.

The foregoing description bore no relationship to the stage of the menstrual cycle as demonstrated in the corresponding endometrium. There were no endocervical findings characteristic of any stage of the cycle, under either low or high magnification. There was neither constancy of pattern nor consistency in detail at any given phase of the menstrual cycle. Thus, many endocervical biopsies were histologically similar, and yet their corresponding endometria revealed entirely different stages of development. Also, in many instances where endometrial biopsies were microscopically almost identical, their corresponding endocervices showed extreme differences in appearance. Finally, marked variations were frequently seen on the same slide of endocervix, at all periods of the menstrual cycle.

### Discussion

Evidence of a definite histologic cycle in the human endocervix was produced first by Wollner. Using a Hyams cervical electrode on a cutting current, he coned out specimens of endocervix during the course of the menstrual cycle. In his first investigation,<sup>6</sup> Wollner demonstrated a definite histologic cycle in six of the nine patients studied. In his second report,<sup>7</sup> consisting of fifty-four endocervical biopsies obtained from twenty women, a typical cycle was observed in eight patients. In some cases, however, premenstrual changes were found in the postmenstrual period. These reversed findings were interpreted by Wollner as an indication of hormonal imbalance. In his third study,<sup>8</sup> he correlated for the first time the histologic endometrial and endocervical variations. In a study of four cases, he confirmed his previous findings of definite cyclic changes in the endocervix.

During the postmenstrual phase, according to Wollner, the lining epithelium is low columnar, sharply outlined, with scanty cytoplasm, and nuclei close to the basement membrane. The glands are few in number, widely scattered, narrow, regular in contour, lined with moderately high columnar cells

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Fig. 1 (Case 24).—Early proliferative endometrium, taken three days after onset of menstruation. ( $\times 80$ .)

Fig. 2 (Case 24).—Endocervix, taken three days after onset of menstruation. Note the numerous glands, with papillary excrescences. Compare with Fig. 5, to which it is very similar. ( $\times 80$ .)

Fig. 3 (Case 24).—Endocervix, taken three days after onset of menstruation. Note the varying height of the gland cells and the different positions of their nuclei. Compare its similarity to Fig. 6. ( $\times 400$ .)

Fig. 4 (Case 34).—Late secretory endometrium, taken five days before the onset of menstruation. ( $\times 80$ .)

Fig. 5 (Case 34).—Endocervix, taken five days before onset of menstruation. Note the variation in gland architecture. Compare with Fig. 2. ( $\times 80$ .)

Fig. 6 (Case 34).—Endocervix, taken five days before the onset of flow. Note that the gland has been sectioned obliquely, the resulting superimposition of cells giving increased height to the epithelium. Compare with Fig. 3. ( $\times 400$ .)

endometrium an ordinary semimalleable curette, which had been narrowed and sharpened, was used. For obtaining endocervix, a laryngeal punch on a universal handle was employed. This instrument yielded fairly good specimens of endocervix, much better than those which had previously been obtained with a very sharp, narrow curette. The endocervix, being so intimately a part of the underlying tissue, is not easily separated, and only after considerable practice was it possible to remove specimens good enough for study.

During a six-month period, eighty-six patients were utilized for the investigation. From them 420 biopsies were taken, 210 endometrial and 210 endocervical. Of these specimens, practically every endometrium was suitable for diagnosis. Owing to the difficulty of procuring good endocervical biopsies, however, only 150 specimens were considered acceptable for histologic study. Thus, a total of 300 biopsies was studied, 150 specimens of endocervix with their corresponding specimens of endometrium.

### Results

Of the 150 specimens of endometrium examined microscopically, approximately half were proliferative and half secretory. Histologically, they represented fairly evenly the various stages of development observed during the ovulatory menstrual cycle, from the earliest proliferative type seen at the end of flow, to the latest secretory pattern, found at the onset of menstruation. Almost always, the appearance of the endometrium coincided accurately with the picture one would expect to see at that particular time of the menstrual cycle. The few exceptions were those in which an early secretory endometrium was found at the end of the cycle.

The 150 specimens of endocervix presented a variety of histologic patterns, depending mainly upon the angle at which the tissue was sectioned. The lining epithelium, being continuous with that of the glands, showed the same differences and the same likeness as were found in the glandular epithelium. Thus, the epithelium of both lining and glands consisted of tall columnar cells, the height of which varied from slide to slide, and even on the same slide. Their basement membrane was almost always sharply defined. Their nuclei were dark, oval or spindle in shape, with their long axes parallel to those of the cells, except when compressed into dislike shapes against the basement membrane. The nuclei were usually located basally, sometimes centrally, occasionally toward the free surface. Frequently, where the lining was thrown into folds, or where the glands were invaginated into pseudopapillations, the nuclei were piled up irregularly. Now and then, all these types of nuclear arrangements could be seen in the same gland or in the intact lining membrane. The glands varied in size, some being much larger than others, even on the same slide. Thus, the number of glands in each field differed to a great degree. They also varied in shape, some being wide and short, others long and narrow. Some glands were round and of regular contour, whereas others were tortuous and irregular, some showing extremely numerous papillary excrescences. The latter appeared wherever the basement membrane was invaginated into the lumen of the gland. In the excrescences the superimposed cells often gave a "honeycomb" appearance, with their nuclei conglomerated far below into irregular tiers above the basement membrane. The papillary excrescences were interpreted, not as an expression of cellular proliferation, but rather, as a manifestation of uneven sectioning of compound racemose glands. This is demonstrated by observing a gland, in one segment of which the cells are arranged regularly, while in the opposite segment they are piled one on top of the other into a tuftlike projection. It would seem that proliferation, if it existed, would not be present in some part



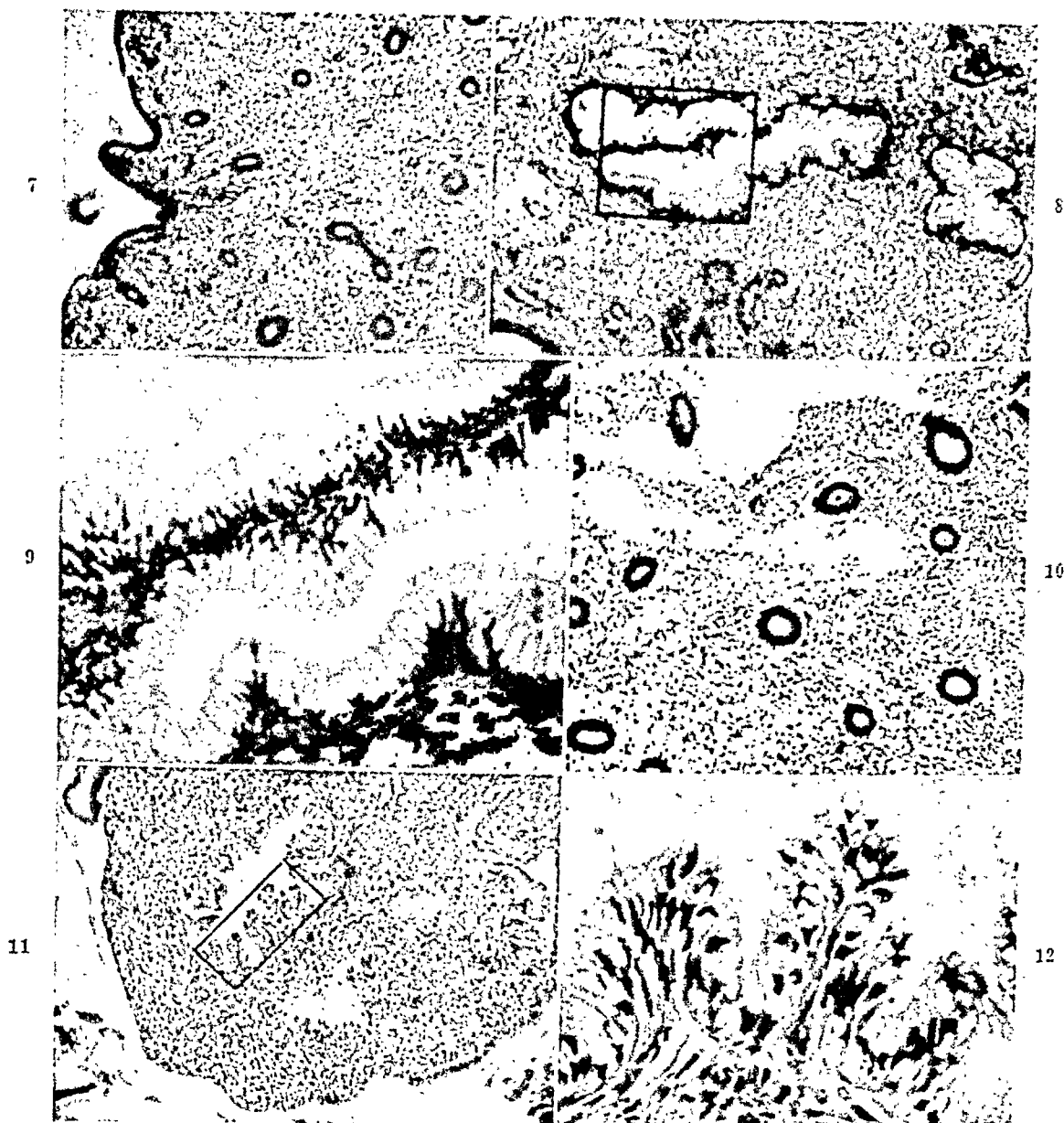


Fig. 7 (Case 38).—Early proliferative endometrium, taken four days after the onset of flow. ( $\times 80$ .)

Fig. 8 (Case 38).—Endocervix, taken four days after the onset of menstruation. Note the many excrescences, even at this very early period in the cycle. Observe its similarity to Fig. 17. ( $\times 80$ .)

Fig. 9 (Case 38).—Endocervix, taken four days after the onset of menstruation. Note how it differs from Fig. 12, although both specimens were taken at the same stage of the menstrual cycle. ( $\times 400$ .)

Fig. 10 (Case 66).—Early proliferative endometrium, taken seven days after onset of menstruation. ( $\times 80$ .)

Fig. 11 (Case 66).—Endocervix, taken seven days after onset of menstruation. Note that the nuclei in the gland are located basally, centrally, and irregularly, depending upon which segment is observed. ( $\times 80$ .)

Fig. 12 (Case 66).—Endocervix, taken six days after the onset of menstruation. Compare the tuftlike invagination of epithelial cells to that of Fig. 15. Note the irregularity in the size of the cells and in the shape of the nuclei owing to the angle at which the gland was sectioned. ( $\times 400$ .)



(See legends on opposite page.)

whose nuclei are close to the basement membrane, with no evidence of secretion in the lumina. The stroma is dense and fibrous, with widely spaced cells of scanty cytoplasm, almost filled by small nuclei. The blood vessels are collapsed. During the course of the menstrual cycle there occur progressive qualitative and quantitative changes in these three mucosal elements, these changes culminating at the end of the premenstrual phase. At this time, just before menstruation, the lining cells are very high columnar, irregular in outline, with spindle-shaped nuclei crowded together. At this stage the glands are most numerous, are densely crowded, irregular, with profuse branching and papillation. They are much wider than before, and consist of high columnar cells bulging into the lumina, which now contain secretion. Owing to the increase in size and number of the glands, the stroma is diminished in quantity, but the stromal cells are larger and contain more cytoplasm. The blood vessels are engorged and edema is present. With the onset of menstruation there occurs extensive destruction of tissue, with complete denudation of the lining epithelium. Rapid regeneration follows, by proliferation of the glandular epithelium over the denuded surface, so that by the sixth day after the beginning of flow, epithelization is complete.

The work of Sjövall<sup>9</sup> also demonstrated cyclic histologic changes in the human endocervix, but of a different nature. He studied thirty-four cases, in different phases of the menstrual cycle, for correlation between endometrial and endocervical changes. The specimens were obtained by operation or autopsy. Although he stated that the glands vary in number, tortuosity, and length, depending upon the area from which the section was taken, how the specimen was cut, and from whom it was obtained, Sjövall nevertheless observed marked epithelial changes during the course of the cycle. During the early proliferative phase, beginning a few days after menstruation, the epithelium starts to grow. In numerous glands the cell multiplication is evidenced by the crowding of the nuclei, which in some places are markedly longer. At this stage gland papillation first begins to appear. During the late proliferative phase, although the intensity of reaction varies from case to case, proliferation of cervical glandular epithelium is pronounced. Everywhere the glands show irregular contours with extensive papillations. The cells are tall cylindrical and very densely arranged. In the papillary excrescences the band-shaped nuclei appear as dense brushes, in which some nuclei are pushed slightly ahead of others. During the early secretory phase epithelial proliferation is best developed, and it reaches excessive proportions. Papillation is now most marked. The gland surfaces and the basement membrane become more irregular, while the nuclei, although still located near the basement membrane, become very long and narrow. During the late secretory phase the papillations undergo gradual regression, until finally they almost disappear. Just prior to flow some specimens show a diminution in the number and extent of development of papillary excrescences, with shorter, more widely separated nuclei, while other specimens show a regression to an indifferent pattern, with papillations almost gone. Thus regression to the starting point is completed during the last part of the secretory phase, and results in the same picture that is seen at the beginning of the cycle. During menstruation the epithelium is fairly high, with round or short cylindrical nuclei located at the base of the cells and not very densely arranged. The epithelial outline is smooth and regular, and papillation is rare. Mucus is secreted throughout the entire cycle. The changes in the surface epithelium correspond to the cyclic changes found in the epithelium of the glands. There is no desquamation of the lining membrane during flow, nor any indication of active formation of new cells. The stroma, which during the proliferative phase is loose, vascular, and relatively cell poor, becomes during the late

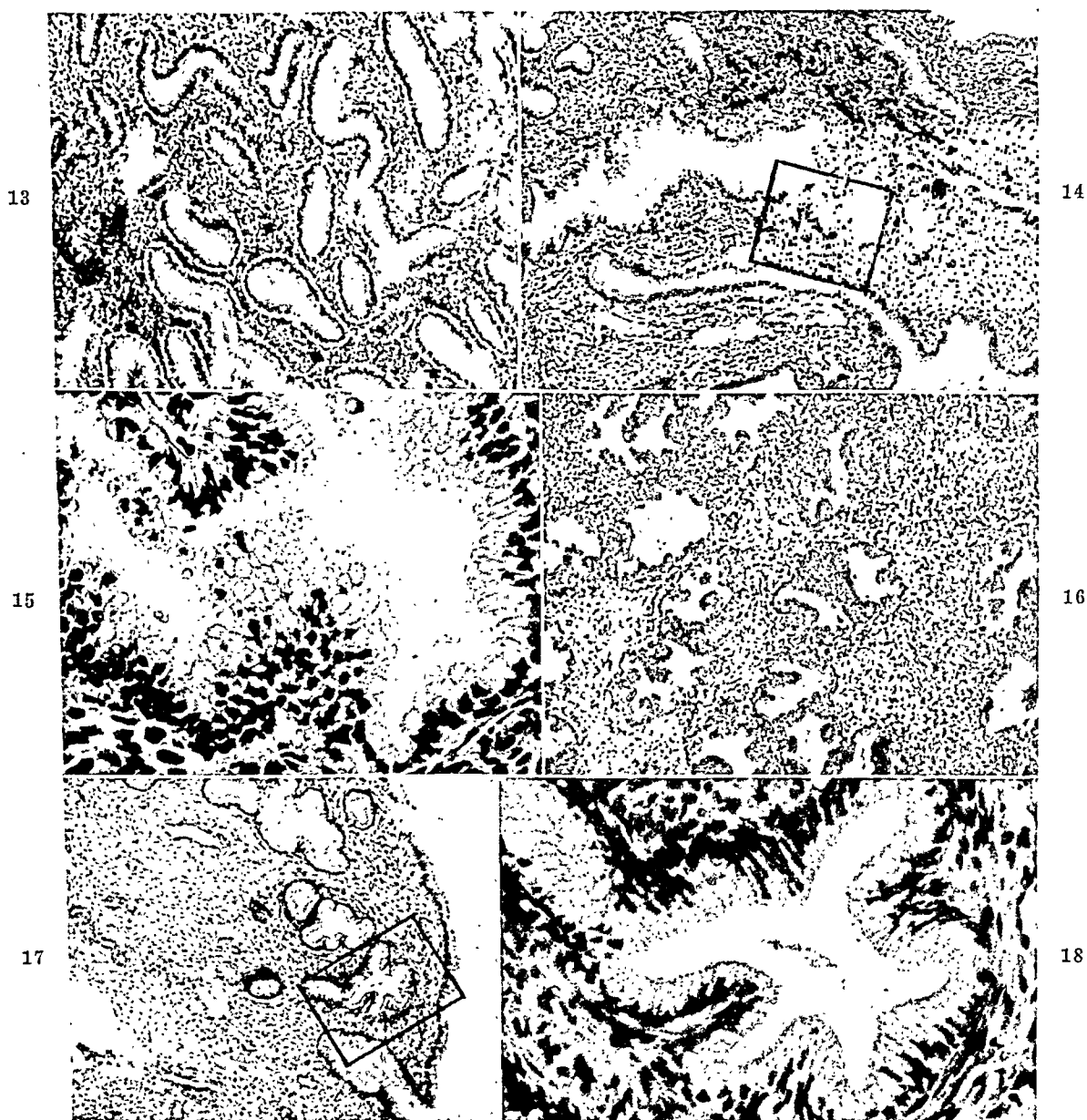


Fig. 13 (Case 17).—Early secretory endometrium, taken eight days before the onset of flow. ( $\times 80$ .)

Fig. 14 (Case 17).—Endocervix, taken eight days before the onset of menstruation. In the gland with the inset the nuclei are located basally, centrally, and in irregular tiers in the cell excrescences. ( $\times 80$ .)

Fig. 15 (Case 17).—Endocervix, taken eight days before the onset of menstruation. Note the juxtaposition of cells sectioned perpendicularly to their long axes, to give a "honeycomb" appearance. The tuftlike protrusion of cells in the upper part of the gland is similar to those seen in Fig. 12. ( $\times 400$ .)

Fig. 16 (Case 67).—Late secretory endometrium, taken at the onset of flow. Note the presence of edema and hemorrhage. ( $\times 80$ .)

Fig. 17 (Case 67).—Endocervix, taken at the onset of flow. Note the intact lining membrane, the absence of congestive changes or devitalization of tissue. Note its similarity to Fig. 8. ( $\times 80$ .)

Fig. 18 (Case 67).—Endocervix, taken at the onset of flow. Note its similarity to Fig. 9. ( $\times 400$ .)

secretory phase compact and cellular. In cases of endometrial hyperplasia the papillary excreescences in the glands became exaggerated, whereas in secondary amenorrhea, of even short duration, the absence of papillations is very noticeable. Thus, Sjövall found the culmination of proliferative changes to occur not at the end of the cycle, as did Wollner, but in the middle of the secretory phase. He suggested that the marked glandular proliferation occurring in midcycle might explain the increase in cervical mucus which takes place at the time of ovulation.

This present study has demonstrated that at any given phase of the menstrual cycle, as determined by the endometrial pattern, there exists in the microscopic sections of the cervix a variety of widely different pictures. These differences are not infrequently seen on the same slide. There is no uniformity of pattern or detail. These normal variations may be caused by several factors, but it is believed that there are two major reasons. The first is the complexity of the compound racemose glands, which would present different pictures even if they possibly could be sectioned in perfectly parallel planes. The second reason is the angle at which the tissue is sectioned, resulting at times in the most bizarre patterns and the greatest irregularity in cellular detail. Thus, whether the glands are wide or narrow, short or long, straight or tortuous, regular in contour or full of excreescences will depend on which segment of the gland the microtome cuts across and at which angle to the gland it does so. The variation in the gland cells is best seen in those glands sectioned in their long axes. Here, in the same branching gland, may be seen cells which are regular in outline and moderately high columnar, cells which are arranged in a disorderly manner and compressed into very high narrow columns, cells which are cut perpendicularly to their long axes to give a so-called "honeycomb" appearance, and cells which are cut obliquely to their long axes so as to be superimposed one upon the other and give the appearance of being exceedingly tall columnar. These normal variations are present throughout the course of the menstrual cycle; they are no more prevalent in one phase than in the other. No type of variation was considered indicative of increased cellular activity or lack of activity. The only constant feature in all the endocervical specimens was the presence of secretion in the lumina of the glands. This could be seen, to a greater or less degree, in almost every gland examined under high magnification.

### Summary

1. A series of 420 biopsy specimens, 210 endometrial and 210 endocervical, was accumulated from eighty-six normal, nonlactating women during various phases of their menstrual cycles, beginning after their first postpartum menstrual period and ending six months later. These specimens were procured concomitantly.

2. Of the 210 endocervical biopsies, only 150 were considered to be histologically suitable for study. The corresponding 150 specimens of endometrium were all acceptable. Thus, a total of 300 biopsies was used for study.

3. Of the 150 specimens of endometrium, approximately half were proliferative and half were secretory, representing equally the different stages of development found during the ovulatory menstrual cycle.

4. A description of the histologic appearance of the endocervix during the menstrual cycle is given. The relationship of this appearance to the cyclic changes in the endometrium is considered.

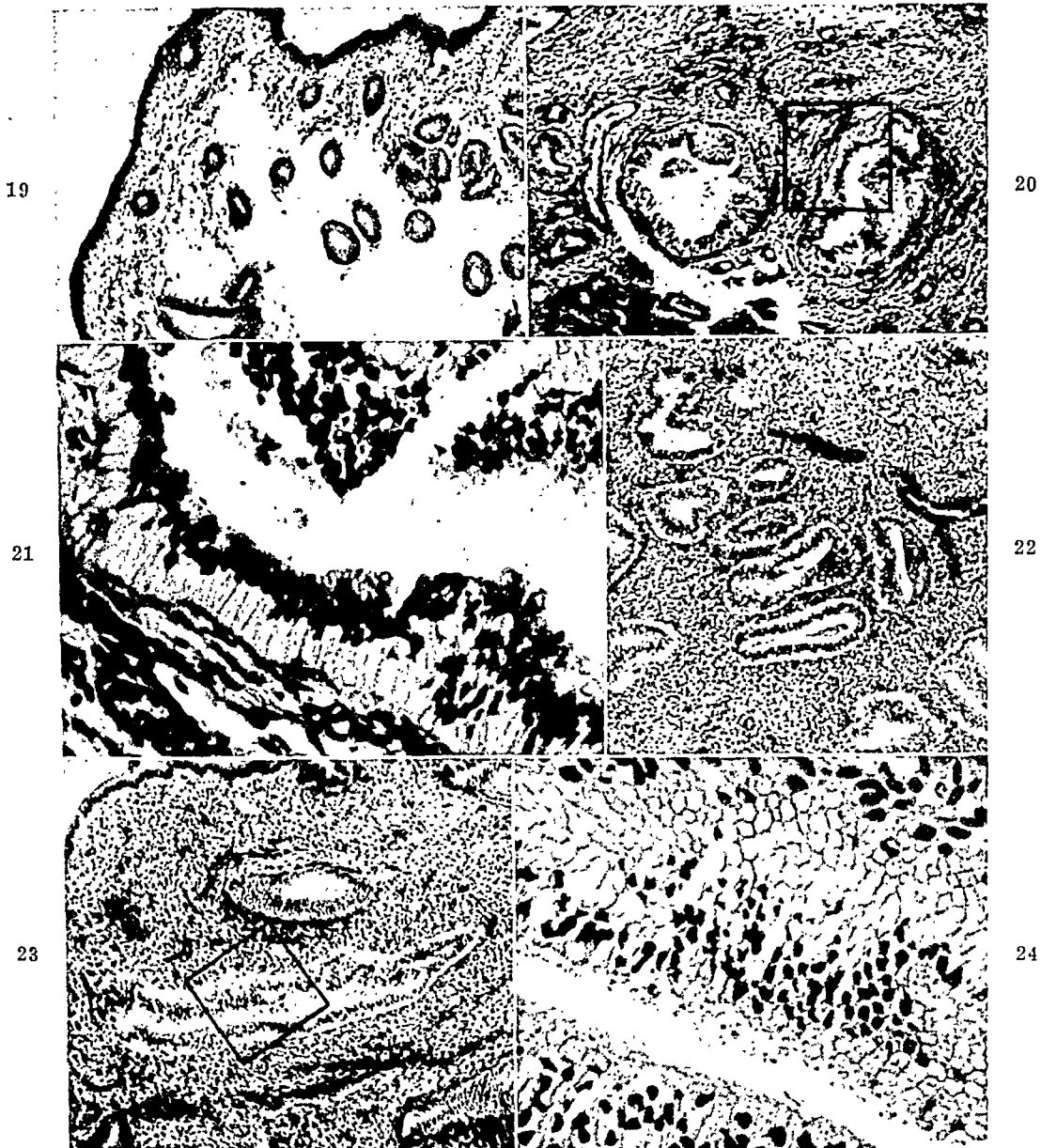


Fig. 19 (Case 87).—Early proliferative endometrium, taken eighteen weeks post partum during lactation amenorrhea. Onset of first menstruation two months later. ( $\times 80$ .)

Fig. 20 (Case 87).—Endocervix, taken eighteen weeks post partum during lactation amenorrhea, with a sharp curette. Note the piling up of cells and the location of the nuclei near their free margins in both lining and glands. Note the similarity to Fig. 23. ( $\times 80$ .)

Fig. 21 (Case 87).—Endocervix, taken eighteen weeks post partum during lactation amenorrhea. Note the "honeycomb" appearance of the cells in the papillation at the right upper angle of the photograph. Note its resemblance to Figs. 15 and 24. ( $\times 400$ .)

Fig. 22 (Case 58).—Early secretory endometrium, taken fourteen days before the onset of menstruation. ( $\times 80$ .)

Fig. 23 (Case 58).—Endocervix, taken fourteen days before the onset of flow. Note the absence of papillary excrescences. Also note the position of the nuclei in lining and gland cells. Compare with Fig. 20. ( $\times 80$ .)

Fig. 24 (Fig. 58).—Endocervix, taken fourteen days before the onset of flow. The superimposition of cells and the "honeycomb" appearance are caused by tangential section of the gland. Compare with Fig. 21. ( $\times 400$ .)

## DEXEDRINE AND WEIGHT CONTROL IN PREGNANCY\*

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THE control of weight during pregnancy is one of the important aspects of prenatal care. Obesity in the nonpregnant patient is a serious threat to health since it predisposes to diabetes, cardiovascular-renal diseases, and definitely shortens the life span of the individual.<sup>1</sup> The addition of pregnancy may increase the obesity, which, it is claimed, may predispose the patient to dystocia, prolonged labor, and toxemia.

Many methods for weight reduction have been used, with varying results. The oldest and simplest is diet. Also commonly used are catharsis and/or diuresis, but these have obvious objections. Atropine sulfate had its advocates who claimed that by drying mouth secretions, it reduces the appetite. Its effect, however, is not always predictable, and its use is not free from danger. Various emetics and nausea-producing drugs have been tried and discarded. The introduction of dinitrophenol was heralded as a panacea for obesity, but, with its widespread use, its toxic effects were soon discovered, and the drug was condemned.

The mention of desiccated thyroid for weight reduction arouses a controversial storm. Its widespread use only serves to emphasize the warning by the Council on Pharmacy of the American Medical Association against the "fallacy and dangers of overstimulating the body with thyroid."<sup>2</sup> It is indicated only in hypothyroid states, and its indiscriminate use should be deprecated.<sup>3</sup> Thyroid increases the appetite, does not always reduce weight, and is toxic in many cases.

Medical consensus holds that most obesity is psychogenic in origin. The old idea of "glandular imbalance" was exploded by Newburgh<sup>4</sup> and others<sup>1</sup> who showed that obesity is simply due to excess caloric intake in relation to caloric expenditure for a particular individual. Psychic factors which may result in constant overeating are variable and include emotional tension, fear, anxiety, frustration, a feeling of insecurity, monotony, and subconscious factors due to infantile personality, such as the urge for oral gratification. Pregnancy, with its multiplicity of new and varied experiences, usually intensifies these emotions.

Therefore, any drug which could decrease appetite, stimulate the patient mentally and physically, reduce boredom, raise "morale" and be relatively non-toxic would be the ideal choice for weight control. Dexedrine sulfate fits this picture fairly well.† Dexedrine sulfate is dextrorotatory amphetamine sulfate,

\*Presented at a meeting of the Chicago Gynecological Society, Oct. 15, 1948.

†Dexedrine is the proprietary name for dextrorotatory amphetamine manufactured by Smith, Kline and French Laboratories. The name Dexedrine will be used in this report for the sake of brevity.



5. A résumé of the cyclic endocervical changes reported by Wollner and Sjövall is presented.

### Conclusions

1. The human endocervix presents histologically a variety of pictures, this variation being the result of the complexity of the endocervical glands and the angle at which they are sectioned.

2. These different pictures cannot be correlated with the cyclic changes in the corresponding endometriums.

3. Specimens of endocervix presenting very similar histologic pictures are often associated with specimens of endometrium exhibiting extreme differences in their stages of development.

4. Specimens of endometrium showing identical microscopic patterns are frequently associated with specimens of endocervix which are entirely different in appearance.

5. The endocervix does not undergo cyclic changes which are demonstrable by ordinary histologic study.

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After a period of weight loss, the drug was discontinued and in many instances, no further treatment was necessary because of the development of new eating habits. It was noted that the use of Dexedrine for a period of four to eight weeks produced a tolerance to the drug in some patients. After a rest period of one to two weeks, this tolerance disappeared and the drug again became effective in reducing appetite.

For a control series, 200 consecutive obstetrical patients were taken from the years before Dexedrine was used and their total weight gain averaged. Sixty-nine of these patients were on 1,200 calorie diets, and thirty-nine took varying amounts of thyroid.

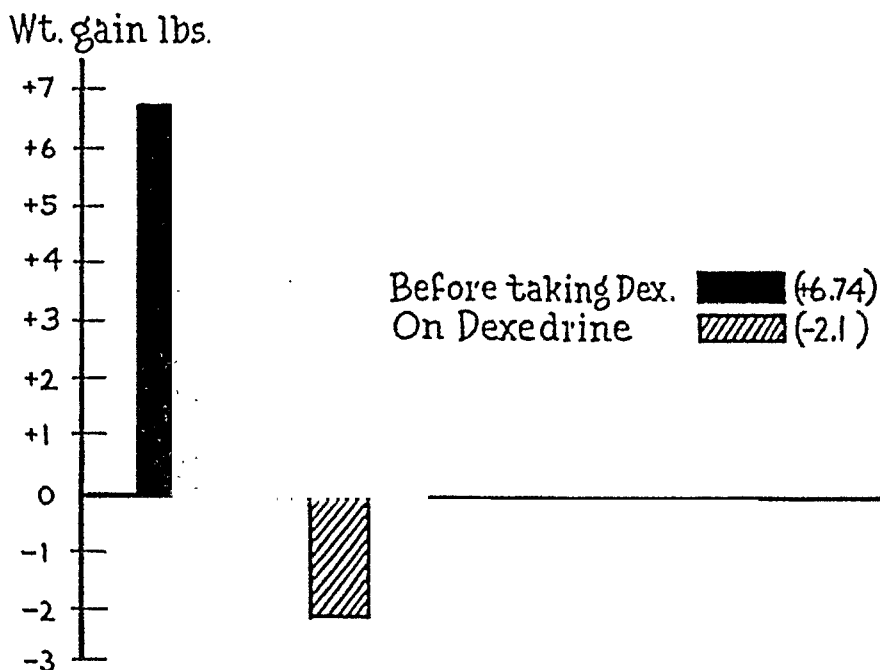


Fig. 1.—Average weight gain during four-week period.

When this series was begun, it was not the purpose of the treatment to reduce obese patients during pregnancy, but rather to control their weight gain. Toward the end of the series, it became apparent that obese patients could safely reduce during pregnancy with the use of Dexedrine, either by starting the drug prophylactically early in pregnancy or using larger and more frequent doses. Finch,<sup>10</sup> using larger doses of Dexedrine, reported an interesting series in which the weight of seventy obese, pregnant patients was controlled with Dexedrine. Eight weighed less at delivery than at the onset of pregnancy. He concluded that Dexedrine is a valuable and safe drug to use in preventing excessive weight gain in obstetrics.

### Results

Twelve of the 100 patients who received Dexedrine began its use at the first prenatal visit. In the remainder of the patients, a comparison of weight gain during a four-week period prior to taking Dexedrine, but on a 1,200 calorie diet, showed an average gain of 6.74 pounds for each patient, the smallest being 4 pounds and the largest, 12 pounds. These patients, taking Dexedrine during the following four-week period, showed the following: fourteen patients gained one to two pounds; twenty-one remained the same; and fifty-three lost from one to nine pounds. There was an average net loss of 2.1 pounds per patient (Fig. 1).

the racemic mixture being the more commonly known Benzedrine sulfate. Oddly enough, the effect of Benzedrine on appetite was first noted as a side reaction when the drug was used in psychiatry for the relief of depressive states. Numerous reports on its use in the treatment of obesity have since appeared in the literature.<sup>5, 6, 7, 8</sup> Dexedrine has a similar effect on appetite and was considered more desirable than the racemic compound for trial during the prenatal period because it produces fewer side reactions.

Many theories have been proposed to explain the mode of action of Dexedrine in weight control. They include a diuretic action on the kidneys, an increase in the basal metabolic rate and energy utilization, a direct action on the gastrointestinal tract to reduce hunger, and a direct action on the central nervous system to reduce appetite and stimulate activity. However, Harris, Ivy, and Searle<sup>9</sup> and others have shown that Dexedrine has virtually no effect on the kidneys, basal metabolic rate, or gastrointestinal tract. It acts on the central nervous system causing anorexia, with resultant reduction in food intake and also improves the general mood of the patient.

Dexedrine has an extremely low toxicity, and its therapeutic margin is so wide that it can be given safely in man even in doses many times the therapeutic amount.

### Procedure and Methods

The present series covers the years 1945, 1946, and 1947, during which 100 pregnant patients were given varying amounts of Dexedrine sulfate in an attempt to control excessive weight gain. These were all carefully supervised private patients, part of a total of 563 private patients delivered during the period of study. There were fifty-two primiparas and forty-eight multiparas. Of the multiparas, thirty-four had previously been delivered by the author without the use of Dexedrine. Because of excess weight gain in their last pregnancies, the drug was prescribed early in the present pregnancy. This group shows the greatest differential as to weight control.

The drug was prescribed for the balance of the multiparas and all of the primiparas only after usual methods, such as instructions to limit salt and fluid intake, 1,200 calorie diet, and repeated warnings relative to the dangers of obesity failed to produce the desired results.

Twenty-two patients of the total 100 took desiccated thyroid in dosages of from  $\frac{1}{2}$  to  $1\frac{1}{2}$  grains daily, because of low basal metabolic rates, but this did not control their weight satisfactorily, and Dexedrine was also prescribed.

The average dose of Dexedrine sulfate was a 5 mg. tablet taken at 10:00 A.M. and repeated at 3:00 P.M. Some patients subsequently had to double the dose, but no patient received more than a total of 20 mg. daily. The time interval for giving the drug was chosen to gain maximum appetite abatement for lunch and supper, the largest meals, without producing insomnia caused by taking the drug too late in the day. This proved a satisfactory arrangement. All patients were given a diet complete in nutritional requirements except for the total calories which were limited to 1,000 to 1,200. In addition, a capsule containing multivitamins, calcium, and iron was prescribed to supplement the diet and prevent avitaminosis and anemia.

The length of time the drug was taken varied from one to six months. The majority of those patients who did not receive the drug prophylactically began taking Dexedrine at the end of the second or beginning of the third trimester when it became apparent that they had gained weight excessively in spite of repeated warnings and the usual measures previously mentioned.

spite of thyroid and careful instructions as to restricted diets. Many in this group began taking Dexedrine early in their present pregnancies, twelve at the first prenatal visit. Nine weighed the same or less at delivery than when they started. The weight change varied from a gain of 22.5 pounds, to a loss of 5 pounds, or a net average weight gain of 15.2 pounds per patient, compared to 32.9 pounds average gain in previous pregnancies (Fig. 3).

As previously stated, many of the patients began taking Dexedrine about the sixth month of pregnancy when their total weight gain was as much as or in excess of that considered normal for the entire nine months. Fig. 5 shows the normal weight curve compared to the weight curve of a treated patient illustrating the controlling effect Dexedrine has on weight gain.

One patient was an obese primipara with an essential hypertension known to exist prior to pregnancy. She was referred to the author by her family physician because of steadily rising blood pressure without albuminuria. When first seen at twenty-four weeks' gestation, her blood pressure was 172/92 and no albuminuria was present. Her weight was 214 pounds, compared to 182 pounds before pregnancy, a gain of 32 pounds. There was no gross edema. She was given a salt-free 1,000 calorie diet with limited fluids, phenobarbital,  $\frac{1}{4}$  grain three times a day, and Dexedrine. Four weeks later she had lost 9 pounds and her blood pressure was 168/92. The regime was continued with omission of phenobarbital and at term she weighed 188 pounds and her blood pressure was 154/88, a reduction in weight of 26 pounds with a concomitant drop in blood pressure (Fig. 4).

This illustrates an observation reported by others,<sup>10</sup> that essential hypertension associated with obesity responds to weight reduction during pregnancy as it does in the nonpregnant state, and that Dexedrine is not contraindicated in hypertension.

### Discussion

About 30 per cent of the patients said that they felt better, less tired, and were able to carry on their duties with greater ease. When Dexedrine was prescribed early in pregnancy, many of the annoying symptoms of the first trimester such as nausea and physical inertia were alleviated in varying degree, probably due to its antidepressant action. In some patients the results were remarkable.

Almost all of them were grateful for the aid the drug gave them in controlling their food intake, and were happy when contemplating the cosmetic result of weight control.

About 20 per cent complained of a mild irritability which usually disappeared in a few days, even though the drug was continued. It was noted that irritability seemed greatest in those patients taking both thyroid and Dexedrine, so that recently thyroid was discontinued when Dexedrine was begun. Eleven patients complained of insomnia which was easily controlled with mild sedation.

The commonly cited dangers and contraindications to amphetamine are hypertension, danger of habituation in susceptible individuals, and excess nervousness. In this series, as in most reports in the literature, no increase in blood pressure was noted from use of the drug, and, conversely, in hypertension associated with obesity, a drop in blood pressure was noted with weight reduction. Freed and Finch also report similar findings. There was no evidence of habit formation in this small group of patients. However, we agree with the literature that amphetamine should not be given to highly nervous individuals who exhibit a hypersensitivity to the drug.

Many physicians are able to control their patients' weight gain by enlisting their "cooperation," but too often this consists of bullying and threatening them. It is an interesting fact, reported to me by many of these patients, that after such an office visit they will go home and indulge in excessive carbohydrate

The total weight change for the entire pregnancy of the 100 patients taking Dexedrine varied from a gain of 23.5 pounds to a loss of 5 pounds, an average gain of 17.7 pounds per patient, as compared to 26.42 pounds per patient for

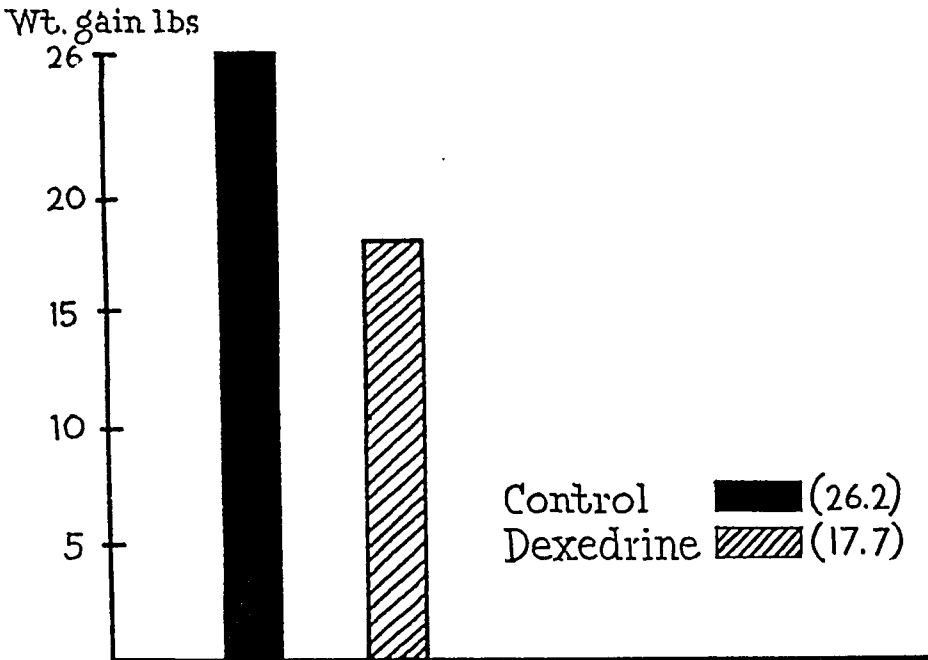


Fig. 2.—Average total weight gain during pregnancy.

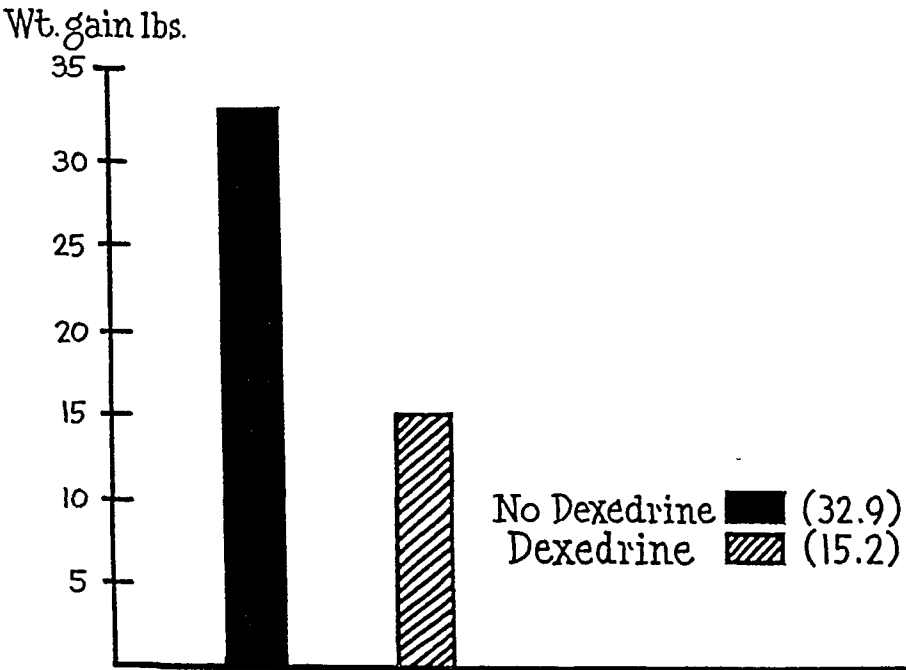


Fig. 3.—Average weight gain of thirty-four multiparas during two successive pregnancies.

the control series (Fig. 2). Thirty-four multiparas in this series had been under the author's care for their previous pregnancies, during which they gained from 25 to 43 pounds total, an average of 32.9 pounds per patient. This occurred in

intake as a result of their own frustration and the animosity aroused by the obstetrician. One may further elicit, with sympathetic questioning, that episodes of excessive weight gain often follow domestic crises.

Luikart<sup>11</sup> reported that no toxemia occurred in 1,000 normal obstetric patients whose weight he was able to control. These were selected cases, however, as those who would not cooperate were omitted from the series. It is just these uncooperative patients who need Dexedrine to aid their attempts at diet control.

In spite of evidence to the contrary,<sup>12</sup> a few men feel that controlling weight gain in the mothers will control size of the babies. Luikart believes this and states that in his series, "There were no large babies. One baby whose parents were both over six feet tall weighed nine pounds two ounces."

In the present series, the babies were of average weight. Six infants, all boys, weighed over 9 pounds. Finch reports that in his group, "The babies were all well nourished and of normal size."

Toxemia merits special discussion. Dieckman<sup>12</sup> states, "Extensive experience has confirmed the belief that excessive and too rapid gains in weight are associated with pre-eclampsia and eclampsia in a high percentage of cases." In his book, however, he adds that Siddall and Mack found no relation between the amount of gain and severity of toxemia and that they found no toxemia in 45 per cent of the normal patients who had gained excessively. Luikart's series of 1,000 weight-controlled normal pregnancies without toxemia has been mentioned.

In the present series, no case of pre-eclamptic toxemia occurred in the treated patients. Four of the multiparas who had gained excessively in their previous pregnancies and developed mild-to-moderate pre-eclamptic toxemia had none in the present series.

It is felt, however, that this series is too small to draw any conclusion as to the relation of obesity to toxemia.

### Conclusions

1. Psychic factors are paramount in producing obesity and these are often multiplied during pregnancy.
2. Dexedrine sulfate is a safe and effective drug to use in controlling weight gain during pregnancy.
3. Dexedrine in dosages effective for the control of appetite has no deleterious effect on blood pressure, and may be used in hypertension.

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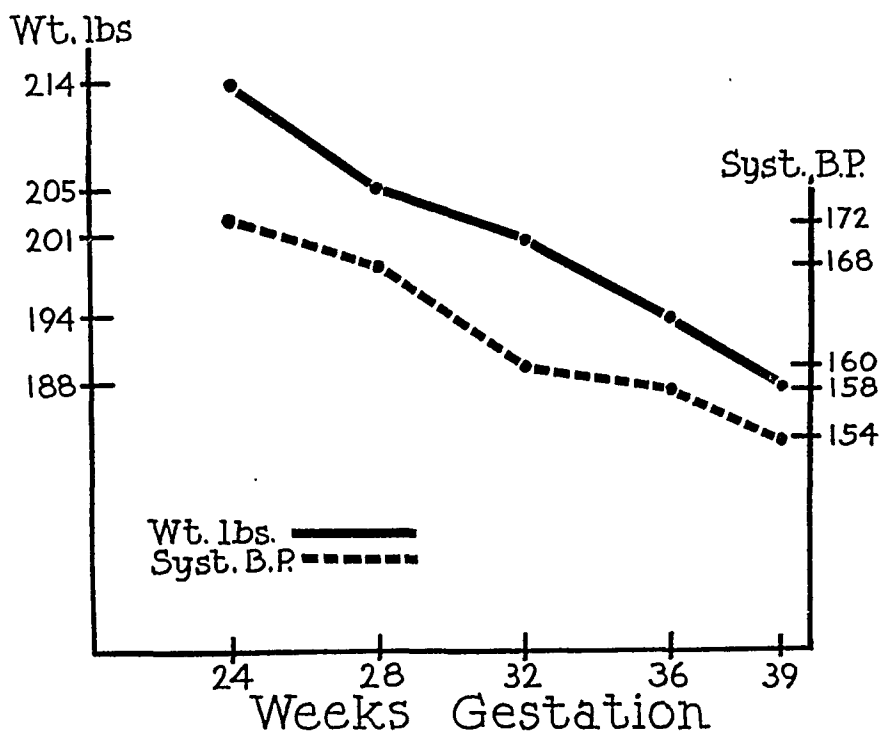


Fig. 4.—Essential hypertension in pregnancy responding to weight reduction with Dexedrine.

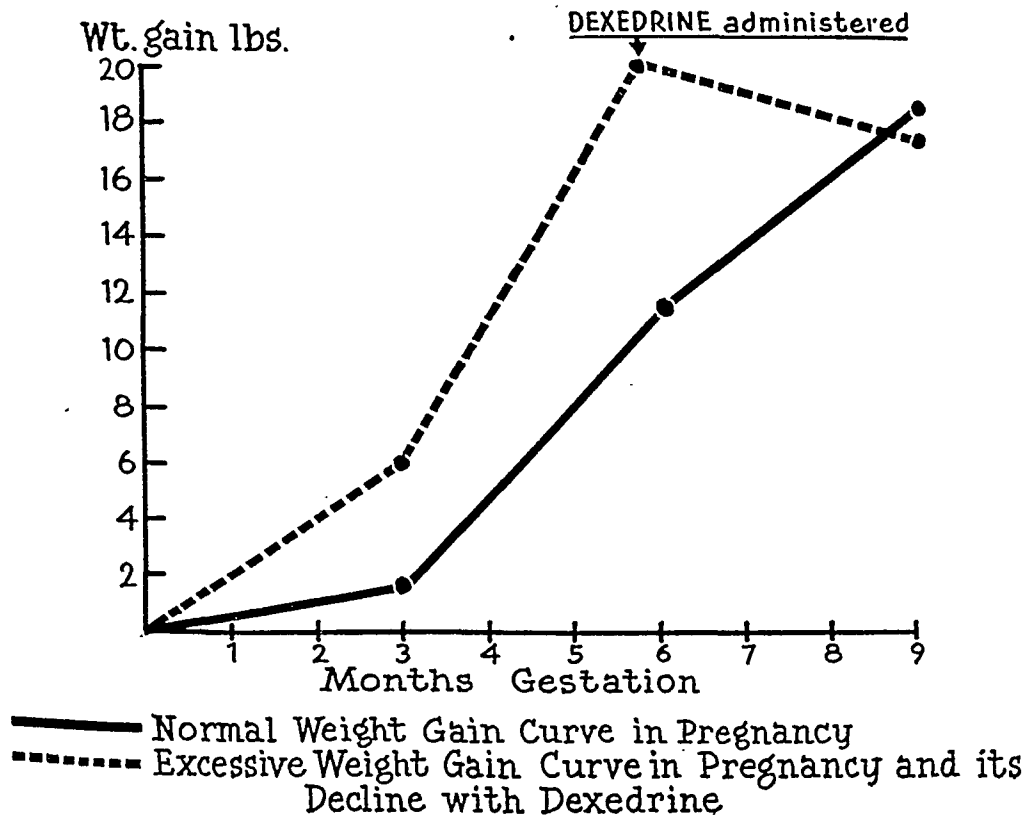


Fig. 5.

neute uterine hemorrhage. The edematous, boiled appearance of the tissue suggested the urgent need of proteins and vitamins, and following their administration her convalescence was rapid and uneventful.

Rigid weight control may keep the patient in good "form." Simple obesity does little harm, but lack of attention to dietary requirements can cause serious disturbances in the mother, the newborn, and the growing child.

DR. M. EDWARD DAVIS.—The control of weight gain during pregnancy is an important phase of good prenatal care. The ideal weight increment for the normal woman has not been ascertained. At the Chicago Lying-in Hospital we try to limit the total gain to 16 to 18 pounds. We make allowance for the woman who starts her gestation weighing less than her optimum amount and allow a greater increase during pregnancy. Likewise, we decrease the weight gain permitted the woman who is overweight. It is important that weight increase be distributed in such a way that about two-thirds the gain occurs during the last trimester of pregnancy, the period during which the fetus grows most rapidly.

Excessive weight gain during pregnancy is a hazard to the mother and her baby. In our clinic Dieckmann has shown that women who gain more than 30 pounds have twice the incidence of toxemias of pregnancy than women who gain less than 20 pounds. Furthermore, the obese woman is more likely to have complicated deliveries resulting in an increased fetal mortality.

It has been our practice to limit weight gain by dietary management alone. Frequent visits to the nutritionist are not always followed by ideal weight control. Often the obstetrician has to read the riot act to the patient in order to accomplish the desired results.

If the use of Dexedrine will aid in the intelligent management of the prenatal patient without harmful results it will be a useful drug. However, larger and more carefully controlled groups of patients will have to be studied to determine its value and its freedom from undesirable complications.

DR. COOPERSMITH (Closing).—Dr. De Costa began as I hoped he would, by saying that obesity is shown to be of importance in obstetrics. I agree with him. Then he began to differentiate between weight gain and obesity which, of course, is important. On the other hand, where does weight gain stop and obesity begin? One shades into the other. In taking care of paras iv and v who weigh about 200 pounds or more, we very often get a history that they gained 30 or 40 pounds with their first pregnancy and they retained 10 or 15 pounds of that, and then they increase in weight with each pregnancy until they come in with their fifth and are obese. If we could get them in their second or third pregnancy, we might prevent the development of obesity.

The role of the physician in weight control has been pointed out. It is that of a father confessor. Those patients who put on excess weight have problems, either about their mothers-in-law, finding an apartment, or with their husbands, and they eat constantly as an outlet. If the physician could spend time with them and talk over their problems, I have an idea we would need less Dexedrine. I think Dexedrine is helpful in controlling appetite and in giving "mental poise." I have had patients come in who had gained excessively in previous pregnancies taken care of by someone else. After they had gained 20 or 25 pounds, they were told, "If you gain more weight you will have to go to another obstetrician." These patients need help, and bullying and threatening them is not the correct approach.

## Discussion

DR. EDWIN J. DeCOSTA.—What constitutes excessive weight gain during pregnancy? A total gain of some 17 pounds will account for the weight of the fetus, placenta, liquor, hypertrophy of the breasts, and increased blood volume. Is weight beyond that excessive? Some authorities maintain that this is so.

What is the objection to so-called excessive weight gain? If the patient is near optimum weight for her age and height at the time of conception, moderate weight gain per se does not appear to lead to dire consequences. When I refer to moderate weight gain, I mean 20 to 30 pounds. Excessive and rapid weight gain may be associated with toxemia but this does not mean that the gain is responsible for the toxemia. Toxemia is often associated with marked fluid retention and consequent weight gain, but toxemia also occurs without weight gain. The most fulminating, severe pre-eclamptic toxemia I have cared for in the past several years occurred in a patient whose full-term weight was only 3 pounds greater than her conception weight. This patient had taken Dexedrine. Her nonpregnant weight was 178 pounds and weight control was primarily for esthetic reasons.

Obese patients, that is, those who are obese prior to conception, particularly those who weigh over 200 pounds, present a variety of problems. Certainly obesity predisposes to heart disease, hypertension, diabetes, poor posture, and orthopedic complaints. During pregnancy these conditions are likely to become exaggerated. In addition, toxemia, postpartum hemorrhage, prolonged labors, malpositions, and large babies are encountered more frequently, and both maternal and fetal death rates are higher than average. However, in Dr. Coopersmith's presentation, he is not specifically concerned with the obese patient. He is only concerned with excessive weight gain as observed during the course of recent or previous pregnancies. This gain I assume is due to fat deposit and not to water retention, as caloric control should not affect electrolytic balance. He has demonstrated his ability to control weight gain by the use of Dexedrine where suggestion and counsel have failed. However, since simple obesity is believed to be psychogenic, induced anorexia and limitation of diet are solely symptomatic therapy and do not reach the underlying cause.

In addition, there is the danger that dietary restriction may lead to inadequate diet, which in turn may result in impaired lactation and bodily function. The generally accepted daily protein requirement during the last trimester of pregnancy is 1.5 Gm. per kilogram of body weight. This amounts to 85 to 110 Gm. of protein. The carbohydrate and fat needs have never been accurately established but accepted amounts generally are carbohydrate, 250 to 400 Gm., fat 70 to 140 Gm. This will provide a diet varying from 2,000 to 3,400 calories. If the patient is to cease gaining or actually lose weight it is obvious that the caloric intake must be something less. Since protein is essential and a diet to be palatable must contain at least 50 Gm. of fat and 150 Gm. of carbohydrate, it is difficult to provide a satisfactory diet of less than 1,400 calories. Dexedrine, by spoiling the appetite, helps the patient to stay on a low caloric diet, but I wonder if we might not err seriously in leaving dietary decisions to these patients. I question whether they would take the kinds of foods they need.

The vitamin and mineral content (calcium, phosphorus, and iron) must be optimum. Mineral and vitamin needs may be at least partially met by supplemental feeding. Recently there has been some indication that water retention may be associated with vitamin deficiency as well as excessive sodium intake. The relationship is involved and includes consideration of progesterone metabolism and liver function in the process of sodium ion mobilization and capillary permeability.

The body's capacity for self-protection is miraculous but when excessive demands are made and protein, mineral, and vitamin needs are barely met, recuperative power can be seriously affected. I have seen poor healing of both abdominal wall and uterus following cesarean section in a patient whose weight was rigidly controlled. Ten days after cesarean section, she had to have a hysterectomy as a lifesaving measure in order to stop



of the patients in this study had four to six before nonsurgical methods were abandoned. All patients had partners whose sperm studies were at or above the recognized minimum requirements. They were put empirically on daily one grain dosages of desiccated thyroid extract, checked by a metabolism test. There were routinely given 0.5 mg. dosages orally of stilbestrol from four days following the end of one menstrual flow to within seven days of expected flow. This was an effort to increase cervical mucus permeability. As well, the patients were instructed to douche shortly before intercourse with Nutri-Sal, a "sperm nutrient" douche. On the advice of several urologists working in the study, the husbands were on from one-half to one grain thyroid daily dosages as well, empirically, despite metabolism readings or total sperm counts. Since the beginning of the study, three husbands have been replaced by donors. There have been two successes.

### Operative Techniques

Actually, a combination of techniques often appeared in the same patient, posing in this fashion some question in classification. For example, one might circumcize the tube on one side, whereas the other tube would require circumcision plus reimplantation. Or, a myomectomy might have to be combined with a resection of endometrial implants, plus fulguration of other implants. Despite these difficulties, the cases are classified by the greatest problem presented in disorder of tubal function, and combinations of techniques are minimized.

1. *Salpingolysis* was required in seven cases, where tubal occlusion had been uncorrectable from below, but which was corrected once the tube or tubes were released from extratubal obstructions. This hampering of tubal function is akin to intestinal obstruction on a like basis, and leaves the tubal lumen undamaged. Care was taken to peritonealize all raw areas meticulously, to be certain that the tubal fimbria maintained their close proximity to the ovaries, and in only two cases was suspension of the tube deemed necessary to prevent readherence in the posterior cul-de-sac. Results in this small group should be deservedly good, for these are indirectly "obstructed tubes."

2. *Salpingostomy* was required in sixteen cases of the group. Two general techniques were employed, either the cuff method of Sovak where the occluded fimbria was removed completely, and then a symmetrical cuff of mucosa was inverted back over the remaining tube, or else the fimbria, if not too badly damaged, was opened as by a dorsal slit on the antimesenteric border (to avoid vascularity and impairment of blood supply) and then the two triangular-shaped flaps were sutured back along the tube. The judgment of the operator dictates the choice.

3. *Probing* open of isthmie obstruction followed by irrigation of the tube with saline using a Chetwood syringe was required in eleven cases. This type of obstruction is suggested by a narrowing of the isthmie portion of the tube and by the finding of small nodules on the serosal surface of the tube, the so-called "chronic isthmie salpingitis" spoken of by the pathologists. Damage to the tubal mucosa is high here, but apparently the results are better if one probes and does not resect this area to reimplant the short distal segment left. This type of occlusion can be relieved very well by insufflation from below at a later date, once the original fibrous closure is relieved by dilatation.

4. *Resection* of the proximal portion of the tube and reimplantation of the distal portion into the uterine cornu were performed in six cases with success in only two. A very real addition to technique in these cases is to open the uterine cavity by a vertical incision into the fundus. The bivalved uterus then can be inspected for the occluded uterotubal junction and then probing can be done from the uterine and not the tubal side. This is of real advantage, for many false passages are made by forcible probing or irrigation of the tube in this

## SURGICAL TREATMENT OF STERILITY\*

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WITH newer methods of diagnosis, sterility studies have assumed a more exact nature. With increased hormone knowledge and potent inexpensive preparations, hormone reinforcement of lagging reproductive effort has become possible and requires no apology. With an adequate male partner, and with an adequate pattern of ovulation, many female patients present themselves still as difficult cases. These constitute by far the most common problems presented in sterility where the female factor alone is at fault. Pre-eminently that fault is tubal occlusion.

Correction of tubal occlusion cannot be handled by hormone attack. It yields either to pressure methods from below, or must be attacked surgically from above. With the use of pressure methods involving either gases or radiopaque media, pressures up to 200 mm. of mercury can be employed safely at monthly intervals for an indefinite period of time. If these procedures are planned for shortly before ovulation is expected, a very satisfactory "take" rate has been reported from many workers in this field. However, those patients who fail to achieve tubal patency by these methods, when they are tried conscientiously and skillfully over an adequate period of time, are left as a hopeless residual for whom surgery seems the only relief.

### Plan of Study

Some six years ago, a routine treatment was established for both primary and secondary sterility patients. This pattern follows closely the sterility work-up regarded as essential and minimal by the American Society for the Study of Sterility. If the male partner is potent, and if the patient is ovulating habitually, with tubal occlusion as the only obvious problem in the case, then she is committed to monthly efforts to relieve this obstruction. The Rubin's test is used as a screening test only and, if on two successive months no gas passes, the patient is next assigned to Lipiodol tubal insufflations. Great care is taken in timing these patients' procedures. Rather than relying upon the basal temperature curve alone, the writer prefers to calculate a fertile phase for each patient, embracing the period of from eighteen through ten days before flow is expected. Ovulation usually comes in the mid-zone of this phase, but variation is given for the few days of sperm life in the vagina before ovulation and the possible life span of the ovum after its release. In other words, the effort is to replenish the sperm supply in the vagina every two to three days during this fertile phase. This may be of more value than withholding exposure until the basal temperature curve shifts upward. Work in artificial insemination techniques would tend to substantiate this impression.

The patient must have a minimum of three Lipiodol uterotubograms *without* progress in tubal dilatation before surgery is considered. The large majority

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three have occluded again and have become refractory to further treatment. In four others, efforts at insufflation had to be abandoned because of either flare-up of the previous (or a new) pelvic infection or because of a chemical peritonitis from iodized oil. These patients responded to chemotherapy but further efforts lie along adoption lines. No deaths occurred.

### Case Histories

It was thought advisable to present a success and a failure in each group with preoperative and postoperative uterotubograms in an effort to analyze the factors in selection of cases for surgery, operative treatment, and aftercare, with causes for failure.

#### *Perisalpingitis.*—

Mrs. G. H., is a 25-year-old housewife, never pregnant, who presented herself as a primary sterility patient of four years' duration. Work-up of the couple was normal except for a 10 cm. left ovarian cyst. Two Rubin's tests were done, but before Lipiodol studies could be started, she had to be operated upon for an acute abdominal emergency because of twisting of the cyst. At operation, a ruptured necrotic dermoid cyst was found, requiring a left oophorectomy. Both tubes were edematous, twice normal size, and bound down to the posterior broad ligament leaves. Other viscera were negative although the patient had had a previous appendectomy as an interval procedure for chronic abdominal pain. Once the fimbriae were mobilized as well as the rest of the tubes, irrigation with saline was performed without difficulty. The patient has since had two pregnancies.

#### *Fimbrial Occlusion.*—

CASE 1.—*Success.* Mrs. M. B. is a 33-year-old housewife, with a sixteen-year story of known gonorrhea. She had had in 1940 a right salpingectomy for a ruptured ectopic pregnancy, and oil later "showed a tumor of the end of the remaining tube." She presented herself first in 1945 because of secondary sterility and chronic left lower quadrant pain. Work-up of the couple was normal with a completely negative pelvis. Four uterotubograms (Fig. 1) are presented demonstrating progressive dilatation of the left tube from occlusion in the midportion on to complete distention of the tube without passage through the fimbria. The last picture of the series shows a left hydrosalpinx without further success in dilatation. Much larger amounts of Lipiodol often will simply sacculate in such a hydrosalpinx without pressure building up to open the fimbria. Interestingly enough, the resected right tube has opened for the proximal half.

At surgery, the right tube was half present. This was opened, circumcised by Sovak's method, and passed saline and probe easily. The left hydro-salpinx was opened, the circumcision was performed by the dorsal slit method. The rugae looked edematous but normal in pattern with minimal scarring. Both ovaries were mobilized from old adhesions and sutured to the round ligaments. Air passed two days later at 110 mm. of mercury. Heavy chemotherapy was continued for two weeks.

The next three x-ray pictures (Fig. 2) demonstrate the postoperative result taken at three-month intervals following surgery. The patient became pregnant two months after the last uterotubogram, eleven months after surgery.

CASE 2.—*Failure.* Mrs. A. P. is a 32-year-old housewife with 12 years' primary sterility. Work-up of the couple was negative except for a uterus about twice normal size with multiple small subserous fibroids. Fig. 3 demonstrates the failure of oil to go beyond the isthmic portion covering five uterotubograms at monthly intervals. At operation, multiple myomectomy was done, with bilateral circumcision of tubes for hydrosalpinx which destroyed the distal half of the tubal mucosal pattern. Resection was performed and a new fimbria created by the dorsal slit method bilaterally. The x-rays in Fig. 4 demonstrate reconstruction of the tubes with eventual passage of oil nine months after surgery. Air passed at pressures of 180 mm. of mercury three days following surgery, and at three-day intervals. The tube has been kept open for two years following surgery with no result.

region where it narrows normally to an extremely small calibre, plus an increased narrowing from the valve found at this end of the tube. If the uterus is opened and the probing is done in the fashion suggested, results in probing open this obstruction have been better. If it cannot be probed open, then the cornual resection of the occluded portion can be done under direct vision and the drawing of the tube through the channel in the uterine muscle and its fixation performed with dispatch. This is of real value. The proximal end of the resected tube is split and each leaf sutured apart. Both successes were delivered by cesarean section because of the possible danger of rupture of any of the three scars. Three cases where vestigial tubal structures were shaped about a ureteral catheter or a tantalum guide were unsuccessful.

5. *Implantation* of the ovary was performed in three cases. There were no successes. Two of these patients had had previous salpingectomies and one had had a tubal ligation for purposes of sterilization. No justification can be given for these cases except that the patient wished surgery despite surgical risk and a virtually hopeless outlook for success. Two of these have subsequently adopted babies. A slice of the uterus was removed from each cornu to expose the endometrium. The Estes' operation was followed except that the ovary was not resected to implant a raw surface into the uterine lumen. Since the ovarian cortex is the site where follicles are found, it seemed unwise to remove this area and to present scarred stroma to the uterine cavity. The ovary was sutured in place. Only one ovary was so treated, the other ovary being left untouched. Cystic degeneration is always a danger in ovaries which are left in a pelvis which has been operated upon. This implantation of the ovary probably does not add to this danger greatly. Since only one ovary was implanted in these three cases, the writer now is struck by his illogical optimism which would hope that the implanted ovary would be the one to ovulate preponderantly.

### Aftercare

Nothing new of significance has been added by the operative techniques outlined so far. These are standard procedures in the armamentarium of every operating gynecologist. It would seem, then, that better results would come only from the aftercare and from this alone. If the tubal physiology is so damaged that it no longer is a conducting mechanism but is merely an inert hollow channel forced open periodically by pressure from below, no amount of aftercare will restore the damaged part. However, here is where optimism focuses attention.

The patients were put on both sulfonamide therapy and penicillin therapy twenty-four hours before surgery, and this was continued for five to seven days after surgery. Forty-eight to seventy-two hours after surgery, the patient was insufflated with pressures up to 200 mm. of mercury. Not infrequently passage of air was noted immediately. In the majority of cases, 77.5 per cent to be exact, this first air insufflation was unsuccessful, due probably to edema of the tube, plus a certain amount of bleeding. Often while one is still operating on the tube, it will become edematous and increase enormously in size. The insufflations are done every three days thereafter until tubal patency is established and maintained for three tests. These tests are interrupted only for menstrual flow. Unfortunately, since the uterus decompresses itself of pressured gas upon the opening of only one tube, often only one tube can be kept open. Following establishment of patency on three successive tests—occasionally false negative results are given during the "spastic phase" of the tube—the patient then has a Lipiodol uterotubogram to demonstrate tubal silhouette and patency. Early in the study, tubal peristalsis was followed using the fluoroscope. This is a valuable procedure. Then, once patency is proved by uterotubogram, Lipiodol studies are done at two- to three-month intervals until pregnancy ensues. Of the group of patients operated upon who did not become pregnant, some twenty-two cases,

The patient was given an adoptive child in the interim and is continuing her effort. A more extensive hydrosalpinx in Case 1 did not result in failure because the tubal mucosa was much less damaged than in either of these tubes, although the over-all dilatation in Case 1 was greater.

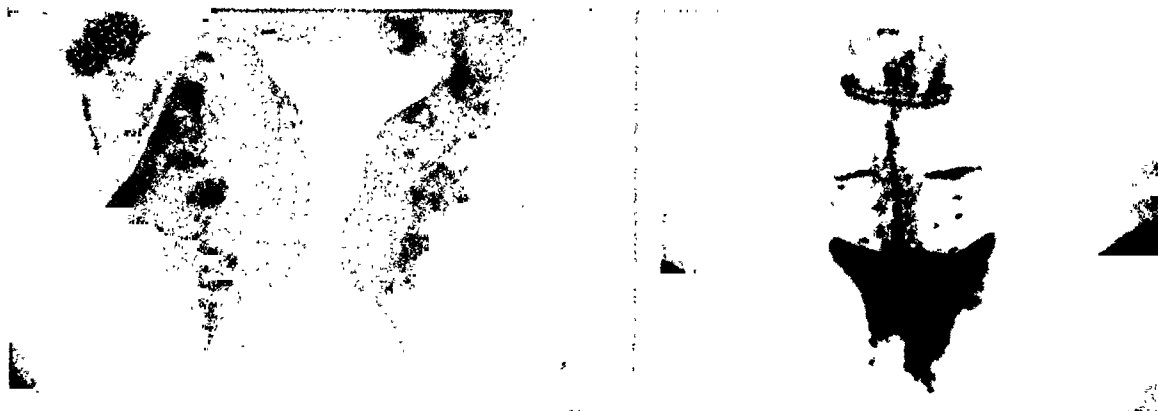


Fig. 3.—Failure to go beyond the isthmus portion over five uterotubograms.

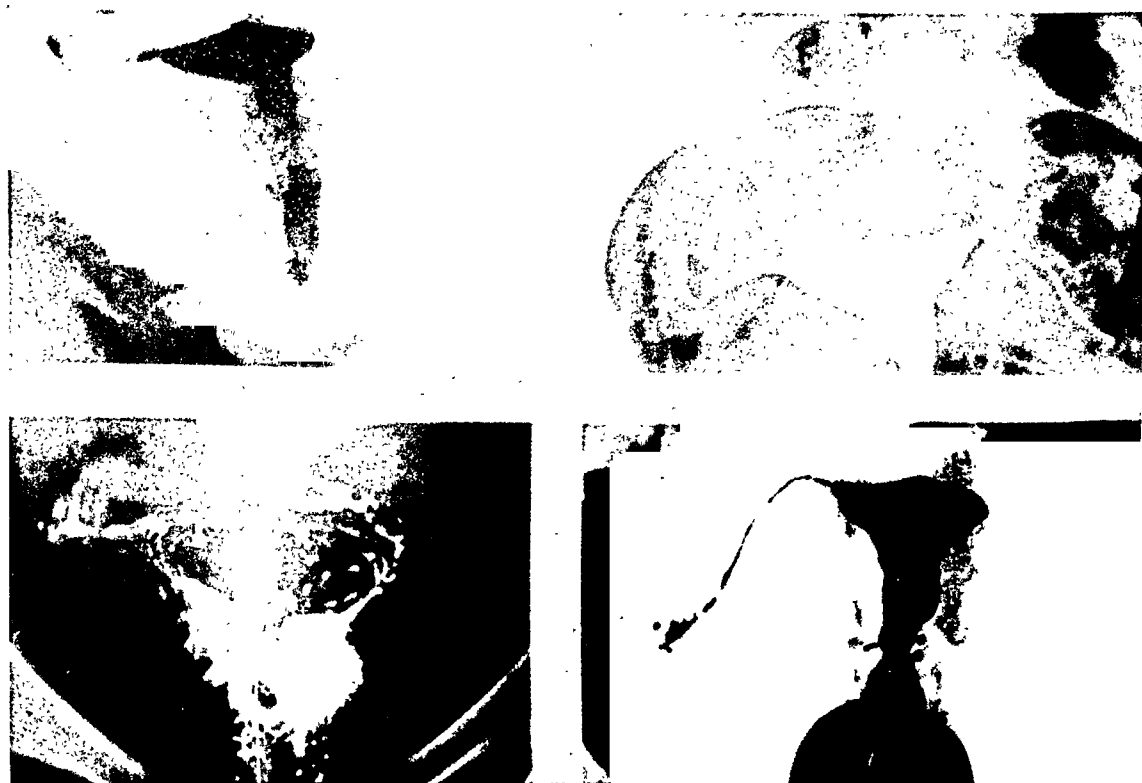


Fig. 4.—Postoperative result showing reconstruction of both tubes, with eventual passage of oil on left nine months after surgery. Tube has been kept open for two years following surgery with no pregnancy ensuing. Hydrosalpinx found at surgery, and destruction of normal tubal architecture and physiology probably cause. A more extensive hydrosalpinx in Case 1 did not defeat pregnancy.

#### *Isthmic Occlusion.—*

CASE 1.—*Success.* Mrs. E. H. is a 36-year-old housewife, married eight years, with an uncorrected spontaneous abortion in 1939. Check-up on the couple was normal but for tubal occlusion. The x-rays in Fig. 5 show the first and last uterotubograms in a series of six

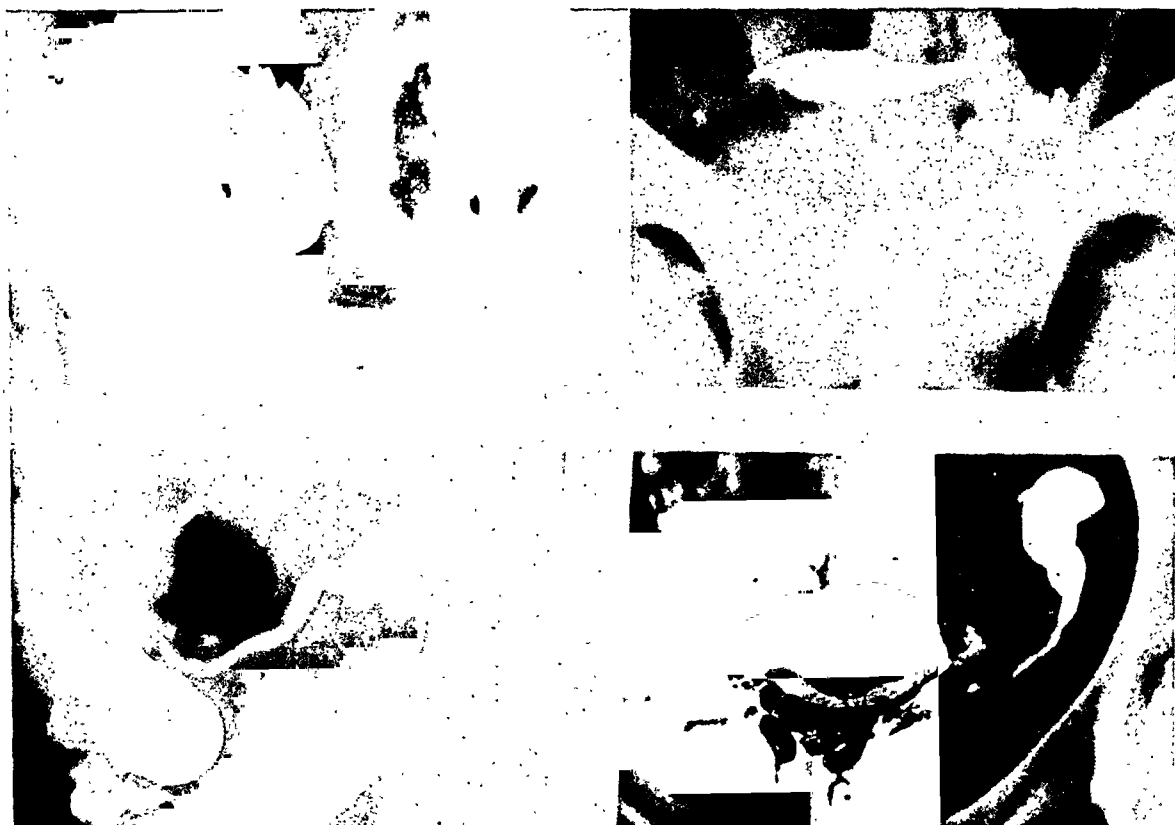


Fig. 1.—Progressive dilatation of left tube from occlusion in midportion on to complete distention of tube producing left hydrosalpinx without further success in dilatation. Right tube (previously resected for ectopic pregnancy) has been opened for first half.



Fig. 2.—Next three x-ray pictures demonstrate postoperative result taken at three-month intervals following surgery. Patient became pregnant two months after last uterotubogram, eleven months after surgery.

over one year with failure to pass beyond the isthmic portion in any. At operation, both tubes were closed in the isthmic portion, but the fimbriae were patent. Both opened on probing and the interstitial portion was normal. Air passed at 180 mm. of mercury on the third postoperative day, and the next x-ray (Fig. 5) demonstrates tubal patency one month after surgery. Pregnancy ensued during the next fertile period. The patient since has had a second normal pregnancy.

**CASE 2.—Failure.** Mrs. M. R. is a 34-year-old nurse, married four years with primary sterility. Work-up of the couple was negative except for bilateral tubal occlusion at the uterotubal junction. The first two x-rays (Fig. 6) demonstrate the first and last uterotubograms in a series of seven over a one-year period with failure to pass beyond the isthmic portion in any. At operation, a bilateral old pelvic inflammation was found with the tubes occluded and adherent in the anterior cul-de-sac. The right tube was completely occluded in the proximal third which was reimplanted under direct vision by bivalving of the uterus, as previously outlined. The left tube was probed open after the fimbria was circumcised, although it had been occluded throughout its entire length. The postoperative x-rays show passage of oil freely on the right which was reimplanted. The left tube which was probed open and circumcised failed to stay open. Failure to achieve pregnancy here is due probably to disorder of physiology subsequent to implantation of the right tube, whose rugae seemed normal but whose innervation may have been impaired in the resection and implantation. She does have a patent channel but its conducting function must be impaired. She is not pregnant as of one year following surgery.

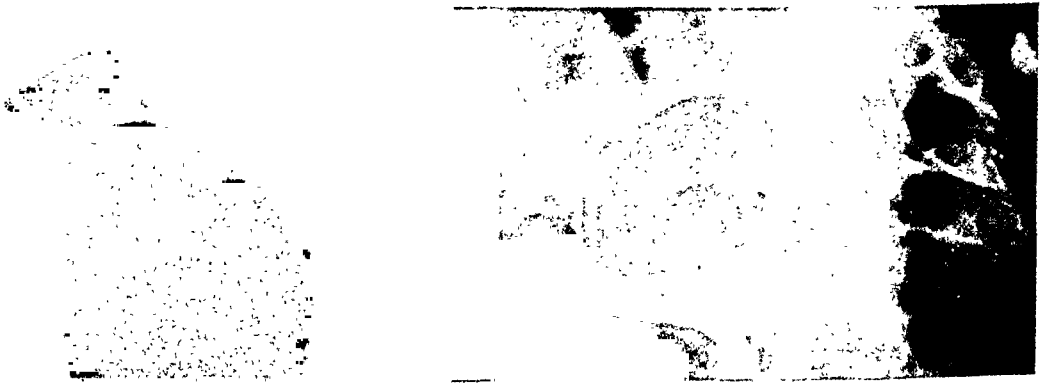


Fig. 7.—First and last uterotubograms over an eighteen-month period demonstrating complete occlusion at the uterotubal junction. The outer half of the right tube was reimplanted. The left tube was probed and irrigated open. Patient became pregnant first ovulation period after surgery, hence no postoperative uterotubograms can be submitted. Since it is impossible to determine if the pregnancy was consummated via the implanted or the nonimplanted tube, the latter must be given the credit.

#### *Interstitial Occlusion.—*

**CASE 1.—Success.** Mrs. D. W. is a 30-year-old housewife with a primary sterility of eleven years. Work-up of the couple was negative but for tubal occlusion. The panel of x-rays (Fig. 7) demonstrates the first and last uterotubograms over an eighteen-month period showing no improvement in the complete bilateral occlusion at the uterotubal junction. At operation, the right tube was closed for the proximal third, was probed open, and passed saline. The left tube was destroyed by old adhesions in the proximal half. This was resected and the normal distal half was reimplanted under direct vision by uterine bivalving. Air passed at 140 mm. of mercury on the third postoperative day. The patient became pregnant the first ovulation period following surgery, and no postoperative x-rays are available as a result. It is impossible to determine if the pregnancy was consummated via the implanted or the nonimplanted tube, therefore the latter must be given the credit.



Fig. 5.—First and last uterotubogram in a series of six over one year with failure to pass beyond the isthmus portion in any. Postoperative result demonstrating tubal patency bilaterally one month after surgery. Pregnancy ensued with the accompanying fertile period. Patency achieved by probe and irrigation.

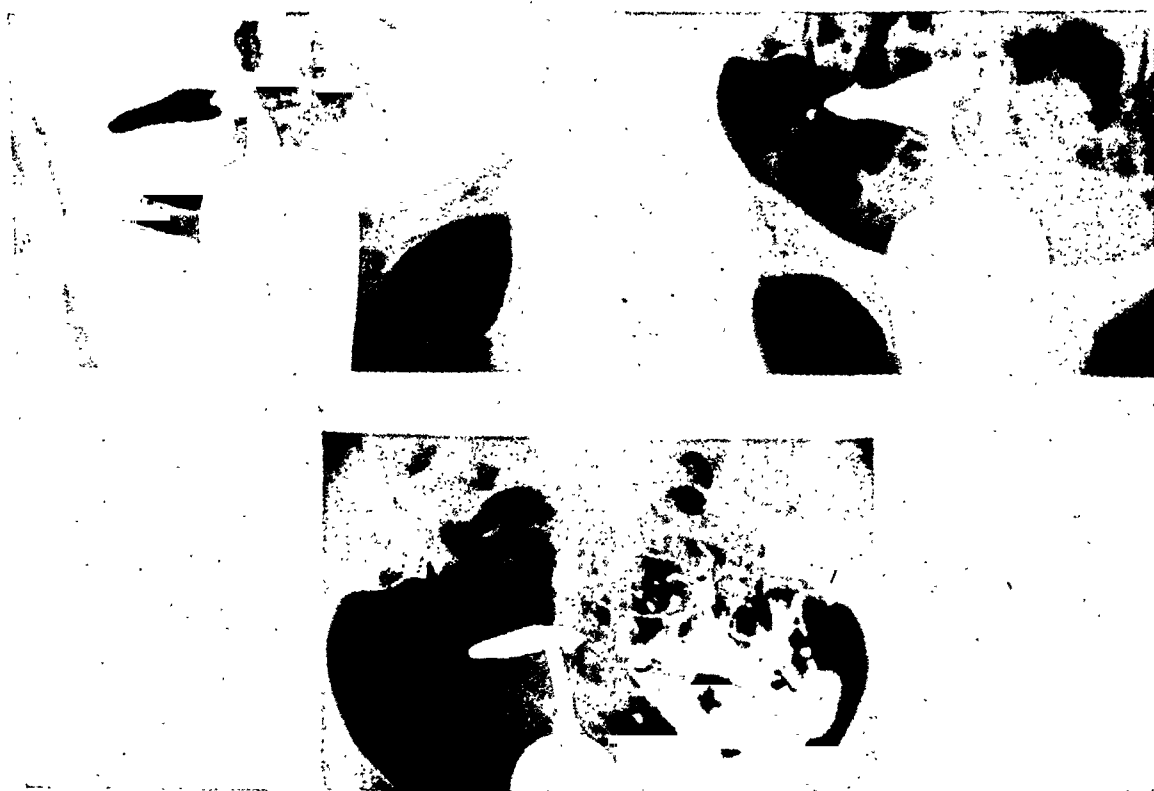


Fig. 6.—First and last uterotubogram in series of seven over one year with failure to pass beyond isthmus portion in any.

Postoperative result demonstrating passage freely on right, the inner third of which was probed open and irrigated, but which was reimplanted because interstitial portion was hopelessly occluded. Left tube was probed open after fimbria was circumcised. This failed to stay open. Failure to achieve pregnancy probably due to disorder of physiology subsequent to implantation of tube.



It was interesting that of the 27 primary sterility cases, only seven gave a specific history of pelvic infection of any kind. It is difficult to evaluate the possible role of the cyclic shedding of the tubal epithelium, possible inspissation of such slough with resultant tubal occlusion. The role of the trichomonas is little known. Very likely the majority of the inspissations are relieved by insufflation methods without there being an adhesive element present. At any rate, one returns to gonorrhea, infection following pregnancies of varying kinds, pelvic pneumococcal infections, occlusions secondary to appendicitis, secondary to cervicitis, and then to an unknown wastebasket of etiological factors.

Of this group, sterility was associated with clinical pelvic inflammation in four cases although in the chronic stage, with endometriosis in two cases, with fibroids in three cases, and with ovarian cysts in two cases. However, all of these cases were screened by air and oil insufflations before surgery. Where malignancy was suspected, or where disordered bleeding or increasing pelvic masses were found, surgery was done immediately. These latter cases are not included in this study.

The results are summarized in Table I.

TABLE I

<i>Number of cases</i>	43	
Primary sterility	27	
Secondary sterility	16	
<i>Types of Obstruction</i> (Classified as the optimum penetration of oil by a minimum of three uterotubograms repeated at monthly intervals)—		
1. Perisalpingitis	7 cases	4 successes
2. Fimbrial occlusion	16	11
3. Isthmic occlusion	11	4
4. Interstitial (uterotubal junction)	6	2
5. Complete (tubes previously sacrificed or requiring removal with implantation of ovary)		0
	—	—
	43 cases	21 successes
<i>Successes</i>	21	or 48.8 per cent
Spontaneous abortions	2	
Ectopic pregnancies	0	
Viable pregnancies	19	or 44.1 per cent
Premature deaths	1	corrected survival rate 41.8 per cent
<i>Average months after surgery to achieve pregnancy</i>	7.4	
<i>Deaths</i>	0	

Summary

It would suggest that surgery has its place in the treatment of tubal occlusion where nonsurgical efforts are of no avail after conscientious and prolonged therapeutic effort has been given. In this series, the best results came in those cases where the least had to be done, as in simple lysis of peritubal adhesions, and next best in uncomplicated closure of the fimbriae. Where there has been disorder of mucosal pattern, impaired blood supply, or where the surgical procedure itself may disorder tubal innervation, results justifiably are poor. The reimplanted segment of tube or the unsupported ovary moored in the uterine wall would give the least good results, admittedly.

**CASE 2.—Failure.** Mrs. M. R. is a 29-year-old housewife whose primary sterility was of ten years' duration. Check-up was normal except for a borderline count (40,000,000 after treatment with thyroid and vitamins) on the part of the husband, and many small subserous fibroids. The first x-ray (Fig. 8) demonstrated the best uterotubogram of five demonstrating ultimate passage to the fimbriae on this, the best. This could not be repeated on three subsequent attempts. At operation, there was bilateral occlusion of the proximal third of the tube, but patency beyond was normal with normal fimbriae. A multiple myomectomy was done with bilateral resection and implantation of the outer two-thirds of the tubes under direct vision. After operation, air passed bilaterally at 200 mm. of mercury on the third day. The postoperative uterotubogram demonstrates free flow with normal tubal architecture. The husband is questionably adequate as a partner. At the end of a year, an adoptive child was given to relieve emotional pressure. Efforts now are under way using the donor technique. Failure here may be on the husband's side.



Fig. 8.—Best uterotubogram of five demonstrating ultimate passage to fimbriae on this, the best, but could not be repeated on the last three attempts.

Postoperative uterotubogram demonstrating bilateral free flow with normal tubal architecture. Husband unquestionably adequate partner. Have adopted child, meanwhile having uterotubograms at three-month intervals. Possible ultimate artificial insemination.

#### *Complete Obstruction.—*

Three patients have been studied in this group, two of whom had had previous bilateral salpingectomy and the other a tubal ligation. No successes are noted, and for obvious reasons no x-rays are presented. The Estes' technique with slight modification has been followed. The writer is to be criticized for having implanted only one ovary in each case, thus diminishing by some percentage the chances of intrauterine ovulation each month. With more sober consideration, his fear of cystic degeneration of the ovaries in their new site may be unfounded, since the original disease process requiring sacrifice of the tubes may cause later cystic degeneration of the ovaries in a high percentage of cases. No attempt is made to review the literature on this procedure, but good results are given in from only two to four per cent of the reported cases. The laparotomy may be defended by the specific request of the patient for an accurate survey of the tubal status. This is possible only by laparotomy.

#### **Results of Study**

In all, 43 patients were operated upon, 27 of whom were primary sterility patients, and the remaining 16 were secondary. These latter cases included past spontaneous abortions, ectopic pregnancy, traumatic abortions, or term pregnancies. Effort was made to establish the etiology of the tubal occlusion by history, but results were remarkably unsatisfactory. Very few of the patients vouchsafed a story of past gonorrhea, infection after abortion (spontaneous or induced), or knew of complications following normal pregnancy. These patients all were private patients and not clinic-type.

## TREATMENT OF THE MENOPAUSE

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(From the Union Health Center)

A LARGE number and variety of therapeutic agents are advocated for the relief of the symptoms of the menopause. This study was undertaken in order to compare the effects of some representative types of such medications on symptoms and vaginal smears of menopausal patients.

### Characteristics of Clinical Series

Two hundred women in whom a clinical diagnosis of the menopausal syndrome was made form the subject of this study. They are members of the Union Health Center, a clinic established to provide medical care for the Philadelphia members of the International Ladies' Garment Workers Union. The general economic, social, and cultural level of this group is perhaps more uniform than that seen in the average clinic and private practice. Each patient had had a thorough medical and gynecological evaluation prior to referral to the endocrine clinic.

TABLE I

AGE	NUMBER OF PATIENTS	PER CENT OF 200 PATIENTS
24-29	4	2.0
30-39	14	7.0
40-49	100	50.0
50-59	79	39.5
60	3	1.5

Age distribution, according to decades, is shown in Table I. Onset of symptoms predated this study by three to five years, on the average. Of the 200 patients, 115, or 57.5 per cent, were married and were living with their husbands. The others were either single, separated, or widowed. No correlation between marital status and severity of symptoms was apparent.

TABLE II

MENSTRUAL STATUS	NUMBER OF PATIENTS	PER CENT OF PATIENTS	AVERAGE AGE
Regular	19	9.5	44.0
Irregular	44	22.0	46.2
Amenorrhea	137	68.5	48.2
Natural	78	56.9	49.7
Artificial	59	43.1	46.4
Panhysterectomy	47	79.7	47.0
Oophorectomy	6	10.15	40.8
Radium	6	10.15	48.8

Table II shows the menstrual status of our patients. Sixty-three were still menstruating, nineteen regularly. Fifty-nine had had an artificially induced menopause, fifty-three by surgical means and six by radiation. The

The justification for surgery then is simple. If all nonsurgical efforts are of no avail, then the patient is given a choice of adoption or of exploratory laparotomy. Earlier efforts to answer these things by peritoneoscopy and culdoscopy were woefully inadequate. Exploratory laparotomy it must be, for only upon careful palpation of the tube, with evaluation of its potential (as well as that of the ovary) can proper surgical correction be undertaken. Adequate chemotherapy and antibiotic therapy must be employed. Finally, meticulous aftercare to insure continued patency of the tubal canal during the healing period must be done, night or day, fair wind or foul. This latter cannot be overemphasized.

In this day of "semi-adoption" procedures, or artificial insemination, more liberty may be taken in surgical attack, either upon the female or the male. These couples are usually well deserving, for they have selected themselves as desirable by their untiring efforts to have a child of their own often long before they have appealed to the sterility expert. However, the male factor must have been evaluated and dispelled *before* surgery and not as a puzzled postoperative routine.

### Conclusions

1. A series of 43 cases of primary and secondary sterility unrelieved by persistent pressure methods is presented.

2. Success in securing pregnancy through surgical effort is graded directly by the amount of disorder of tubal function, of circulation, or of innervation.

3. The hopefulness or hopelessness of the situation can be evaluated only by exploratory laparotomy, if all other factors are normal or corrected. The patient must have an honest and careful recitation of the statistics of failure and of operative loss in advance.

4. Persistent and conscientious aftercare is as important as the proper selection and execution of the surgical technique in continued relief of tubal occlusion. This must begin two or three days after surgery and must follow until pregnancy is achieved.

5. Roughly, four in ten patients so selected may have a child. The remainder at least have the consolation of trying every channel before adoption is undertaken.

6. No successes are reported from implantation of the ovary in the uterine wall.

TABLE IV

MEDICATION	NUMBER TREATED	NUMBER COM- PLETELY RELIEVED	PER CENT COM- PLETELY RELIEVED	NAUSEA		BLEEDING			RELATIVE COSTS OF ORAL PREPARATIONS (EXPRESSED) AS MULTIPLES OF ESTINYL AND DIENESTROL
				NUMBER	PER CENT	INCIDENCE IN ALL PATIENTS	INCIDENCE IN PATIENTS WITH AMENOR- RHEA	INCIDENCE IN PATIENTS CAPABLE OF BLEEDING	
Progynon-DH	81	68	83.9	3	3.7	8.7	6.2	9.6	11
Progynon-B	59	55	93.1	0	0	0	0	0	
Pellets—alpha estradiol	45	43	95.6	0	0	0	0	0	
Bisdehydrodisynolic acid	24	4	16.6	3	12.5	8.33	4.16	8.33	
Meprane	64	52	81.5	4	6.25	29.7	21.9	33.9	2
Diencetrol	98	90	90.8	6	6.1	17.2	7.15	20.7	1
Ephynal Acetate	65	17	26.1	1	1.5	1.5	1.5	1.8	15
Estrone	96	76	79.1	0	0	12.5	7.3	14.1	
Estinyl	138	130	94.2	13	9.4	23.2	14.5	27.6	1
Methylbisdehydrodisyn- olic acid	35	14	40.0	4	11.4	5.7	5.7	6.9	
Premarin	95	91	95.8	4	4.2	11.6	7.4	12.3	4

average age of the nineteen regularly menstruating women was 44 years, 5.7 years lower than that of women with naturally occurring amenorrhea and patients with irregular menses were, on the average, 3.5 years younger than the group with amenorrhea. It would appear, therefore, that symptoms of the menopause may precede disturbances of the menses by at least two years and that complete amenorrhea may be expected in only two-thirds of patients with climacteric symptoms.

Ninety-two and five tenths per cent of patients complained of hot flushes and 50 per cent of headaches. All patients presented symptoms of flushes and/or headaches. The incidence of symptoms is shown in Table III. Qualitative differences in presenting symptoms between patients with artificially induced and naturally occurring menopause were not observed.

### Drugs

It is impractical to study all the preparations available, so that only representative members of each of the large classes were employed. Diethylstilbestrol was not included because it has already been carefully studied, and detailed information concerning its pharmacology and therapeutic effectiveness is in the literature.<sup>1, 2</sup>

The therapeutic agents selected for study are as follows: alpha-estradiol (Progynon-DH), oral; alpha-estradiol benzoate (Progynon-B), parenteral; alpha-estradiol pellet, subcutaneous; bisdehydrodisynolic acid, oral; 3-4 bis (m-methyl-p-propionoxyphenyl)hexane (Meprane), oral; 4:4'dehydroxy-alpha-delta-diphenyl-beta-delta-hexadiene (Dienestrol), oral; ephynal acetate (Ephynal Acetate), oral; estrone, parenteral; ethinyl estradiol (Estinyl), oral; methyl-bisdehydrodisynolic acid, oral; mixed conjugated estrogens-equine (Premarin), oral.

TABLE III

SYMPTOMS	ALL PATIENTS (200)		NATURAL MENOPAUSE (141)		ARTIFICIAL MENOPAUSE (59)	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Flushes	185	92.5	128	90.8	57	96.6
Headaches	100	50.0	69	48.9	31	52.5
Nervousness	45	22.5	33	23.4	12	20.3
Depression	43	21.5	27	19.1	16	27.1
Fatigue	24	12.0	17	12.0	7	11.8
Dizziness	23	11.5	18	12.7	5	8.4
Insomnia	20	10.0	13	19.2	7	11.8
Vague pains	13	6.5	10	7.1	3	5.1

### Methods

Only patients whose symptoms could clearly be ascribed to the menopausal syndrome were included in this series. Psychotherapy, other than that consequent to the dispensation of medication, was avoided in order to eliminate the factor of variable suggestion. Interviews were short and patients were kept to a fairly strict question and answer routine.

In order to minimize hangover effects of one drug upon another, visits were spaced at five- to six-week intervals. The dose of each medication was adjusted until the minimum effective dose was obtained. This was considered to be achieved when all symptoms were relieved, but the patient continued to experience an occasional, fleeting and mild flush. The patient was then given

many instances, these women worked together in the same shop. Symptoms and reactions to therapy were discussed by them at length, and negative suggestion was not counteracted by reassurance on the part of the interviewer. Nausea, as a presenting complaint, was usually relieved by estrogenic therapy.

One of the expected consequences of estrogen administration is endometrial proliferation. Uterine bleeding can hardly be called an untoward effect; nevertheless, it is a reaction one strives to avoid. Irregular uterine bleeding is common during the menopause, and Te Linde and Bennet<sup>6</sup> have pointed out that bleeding during estrogenic therapy may be coincidental. These investigators treated a series of control patients with phenobarbital; bleeding occurred in 6.3 per cent. This figure is higher than in their estrogen-treated group. Table IV shows a higher incidence of bleeding than is reported in most series. Bleeding occurred in eighty-nine of the one hundred fifty-three women with intact uteri. Sixty-six of these reported the presence of a bloody vaginal discharge, whereas twenty-three patients were unaware of bleeding. When bleeding is re-evaluated in terms of therapeutic episodes, each of five to six weeks' duration, the incidence is seen to be much less impressive (Table VI).

TABLE VI

	REPORTED		NOT REPORTED		TOTAL	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Bleeding patients	66	33.0	23	11.5	89	44.5
Bleeding episodes	92	6.05	26	1.7	118	7.75

The study comprises 1,520 therapeutic episodes.

In view of the long duration of this experiment, the high incidence of bleeding on a patient basis is to be expected. Moreover, the character of the study was unavoidably such that the optimum conditions for the development of uterine bleeding were created. As soon as the minimal effective dose of any medication was determined, a new material was dispensed. Because this was frequently started in subtherapeutic dosage, an estrogen-withdrawal effect was produced. This serial administration of drugs makes bleeding very hard to interpret. Doris Phelps<sup>7</sup> maintains that endometrial activity may be influenced by hormonal effects operating several cycles prior to the one in question.

Comparative costs are shown in Table IV. Cost calculations were made on the basis of the maintenance dose required by 100 per cent of relieved patients, and are expressed in multiples of the cost of Estinyl and Dienestrol, which were the most economical of the preparations used.

### Analysis of Therapeutic Agents

Alpha-estradiol (Progynon-DH) is probably identical with the follicular hormone. It is the dehydroxyestrin, resulting from the reduction of keto-hydroxyl estrin (estrone) to a secondary alcohol. It is expensive and 80 to 90 per cent of its potency is said to be lost on passage through the stomach.<sup>8</sup> It appears to be most useful when cost is unimportant and when side reactions to other oral estrogenic preparations develop. Eighty-three and nine tenths per cent of patients treated with doses not exceeding 1.5 mg. were completely relieved. The incidence of nausea and bleeding was lower than with any other estrogen and the sense of general well-being following adequate dosage was pronounced.

Alpha-estradiol benzoate (Progynon-B) is the ester of alpha-estradiol. Esterification plus suspension in oil prolongs its effectiveness without decreasing its potency. Patients were well maintained on weekly doses of Proyn-

a new drug and the procedure repeated. The order of administration was varied from patient to patient and in the same patient in order to minimize seasonal effects and the influence of previous medication. In many instances, the minimum effective dose of a substance was prescribed at a later date in order to verify its accuracy.

Vaginal smears were taken at each clinic visit. Slides were prepared in duplicate, one stained according to the method of Shorr,<sup>3, 4</sup> the other, following the technique of Papanicolaou.<sup>5</sup> Smears were read without information concerning the clinical picture. Comparison of vaginal smear changes with variations in the clinical response was not made until completion of the study. Only those cases in which the diagnosis of cancer was suspected were discussed.

### Results

The comparative effects of therapy, incidence of nausea and bleeding, and relative costs of the preparations used are shown in Table IV. With the exception of Ephynal Acetate, bisdehydrodisynolic acid and its methylated form, 80 per cent or more of patients were relieved completely of symptoms by all the drugs employed. Although many patients showed partial response to Ephynal Acetate, bisdehydrodisynolic acid and its methylated form, complete relief was not obtained in most instances. This may be due to insufficient dosage.

In a study of this kind, it is difficult to achieve adequate levels of each drug in every patient because of the complicating effects of nausea, bleeding, and patient resistance. Following complete control of symptoms with one preparation, change to another was occasionally refused. Furthermore, if the new drug was given in insufficient amounts, it was not unusual for the patient to object to an increase, attributing the return of her symptoms to the medication itself rather than to the inadequacy of the dose. Since the minimal effective dose was not always attainable, response to therapy was estimated on the basis of patients who had obtained complete relief of symptoms. Dose equivalents are listed in Table V.

TABLE V

PER CENT COMPLETELY RELIEVED	DOSES (ONLY DOSES USED IN THIS STUDY ARE CHARTED)				
	PROGYNON-DH	MEPRANE	DIENESTROL	ESTINYL	PREMARIN
0-9					
10-19			0.2		
20-29				0.02	0.625
30-39		1.0			
40-49				0.025	
50-59	0.5	2.0			
60-69			0.5		1.25
70-79					
80-89			1.0		
90-99	1.0	3.0	1.5	0.05	2.5

The incidence of nausea in this series is higher than that usually reported with estrogenic therapy. A drug was considered nauseating when its further use was refused by the patient and when the nausea could be elicited a second time at a later date. Notwithstanding these precautions, the incidence of nausea may be high because of the nature of the patients in this series. In



In our series, however, bleeding was more frequently associated with the use of Meprane than with any other preparation. Since the vaginal smear responses following its use were no more pronounced than with other potent estrogens, we believe that the effect on the endometrium suggested by our figures for bleeding are open to question. Meprane is an economical, well-tolerated, and potent estrogen which may have a useful place in the therapy of the menopause and deserves further investigation with regard to the production of bleeding.

4:4'dehydroxy-alpha-beta-delta-hexadiene (Dienestrol) is related chemically to diethylstilbestrol. It is a potent estrogenic material which is in the same general economic classification as Estinyl. All reports on this material suggest that the incidence of untoward reactions is low. Barnes<sup>20</sup> treated a group of thirteen, and Rakoff, Paschkis, and Cantarow<sup>21</sup> a group of forty menopausal women without producing nausea in a single case on any dose. Sikkema and Severinghaus<sup>22</sup> found the material to be free of nauseating effects in doses of less than 0.5 mg. whereas Finkler and Becker<sup>23</sup> reported nausea in 4.3 per cent of their seventy patients.

In general, atrophic vaginal smears showed the expected estrogenic effect coincident with control of symptoms. This correspondence was noted by Finkler and Becker.<sup>23</sup> Rakoff, Paschkis, and Cantarow,<sup>21</sup> however, report that "the dosage necessary to obtain a vaginal smear response was in most instances considerably higher than the dosage necessary to obtain a good clinical response." In this study the vaginal smear response produced by Dienestrol paralleled very closely that observed in patients treated with Estinyl and Meprane. This was particularly noticeable when these drugs were administered in effective doses to the same patient in turn.

Of ninety-eight patients treated with Dienestrol, 90.8 per cent showed complete relief of symptoms. Ninety per cent of these were maintained on daily doses of 1.0 mg. or less. Dienestrol exhibits potency, ease of administration, relatively low incidence of side reactions, and economy, which makes it a valuable agent for the therapy of the menopause. The general sense of well-being, however, is not marked. This was reflected in the small percentage of patients who specified preference for Dienestrol over other preparations.

dl-alpha-tocopherol acetate (Ephynal Acetate) is the synthetic acetic ester of vitamin E which possesses biological potency equal to the purified naturally occurring vitamin. The rationale for the use of this material in the menopause is not clearly established. It is said that derangement of gonadotropic activity may be associated in some cases with vitamin E deficiency.<sup>24</sup> The steroid nature and chemical configuration of this substance may bear some relation to its purported effects in the menopause. It completely relieved the symptoms of 26.1 per cent of sixty-five patients with doses of 75 and 150 mg. daily. The effect of still larger doses appears to deserve study, since many patients who had been refractory to the lower dose responded to the higher one. Although incompletely relieved, another 26 per cent were improved with doses up to 150 mg. The question of dosage is still equivocal, however, for Hain and Sym<sup>25</sup> reported response to 12 mg. of tocopherol daily and Christy<sup>24</sup> achieved satisfactory relief in twenty-three of twenty-five patients with 10 to 30 mg. daily.

Notwithstanding the large doses used, Ephynal Acetate produced slight nausea in only one patient. No gross bleeding was reported but microscopic bleeding was observed in one case. The presence of blood in this patient's vaginal smear was likely unrelated to the effects of therapy. Even transitory suggestions of toxicity were absent. Ephynal Acetate exerts no significant effect upon the vaginal smear.

on-B, although in some series injections were required every three<sup>9</sup> to five days.<sup>10</sup> Neither bleeding nor nausea was reported, although many patients were maintained on it for as long as three months. Control of symptoms was readily achieved and weekly maintenance doses of 0.33 to 0.66 mg. kept patients asymptomatic.

Alpha-estradiol pellets are crystals of alpha-estradiol compressed into 25 mg. cylinders. Forty-three patients received an implant of 25 mg. and two patients, because of their previous high estrogenic needs, were given two pellets (50 mg.). Forty-three of these forty-five patients were completely relieved of symptoms. Of the two failures, one was a patient who required four times the usual dose of other estrogens. Her theoretical need was for three to four pellets, but she was given two and was only partially relieved. The other patient considered this therapy unsuccessful because of the persistence of headaches, although her flushes disappeared. Her headaches were not menopausal in character; however, because of the equivocal nature of the response, this patient was classified as a failure.

All other patients heartily endorsed this form of therapy. Only women who had been hysterectomized received pellet implantation. Occasionally, evanescent breast pain was reported. No other untoward reactions were observed. The duration of therapeutic response seems to be from four to eight months with an average of six months.

Pellets containing alpha-estradiol,<sup>11</sup> alpha-estradiol benzoate,<sup>12</sup> alpha-estradiol dipropionate,<sup>13</sup> estrone,<sup>6, 14</sup> diethylstilbestrol,<sup>6</sup> and crystalline estrogens from pregnant mare urine<sup>15</sup> have been successfully employed by others. The paucity of untoward reactions to this form of therapy has been repeatedly observed,<sup>11, 13, 14, 15</sup> although Twombly<sup>16</sup> noted a rather high occurrence of breast changes (50 per cent of cases), cervical leucoplakia, and increase in size of pre-existing myomas. Because of the reported high incidence of uterine bleeding,<sup>11, 16</sup> the use of these pellets should be reserved for patients who have had a hysterectomy. The implantation of a pellet in a woman at the time of panhysterectomy may possibly prevent the abrupt onset of menopausal symptoms.

No information as to cost can be given since pellets of alpha-estradiol are not yet commercially available.

Bisdehydrodisynolic acid is synthetic dl-1-ethyl-2-methyl-7-hydroxy-1,2,3,4-tetra-hydro-2-phenanthrene carboxylic acid, an oxidative derivative of d-equinalin. It and its methylated derivative have been used extensively in Europe.

This material is not commercially available and therefore has no price listing. Its use in Europe indicated that it was a potent, well-tolerated drug producing all the physiologic effects of estrogen.<sup>17, 18</sup> Its use in doses of 0.1 to 0.3 mg. gave complete relief to 16.6 per cent of patients and partial relief to an additional 33.2 per cent. In no instance did the beneficial effects of therapy persist longer than twenty-eight days after the medication was withdrawn. Nausea developed in three, and abdominal pain in two of twenty-four patients. Two patients complained of vaginal spotting.

In the doses used, bisdehydrodisynolic acid appeared to be relatively inefficient in controlling menopausal symptoms. The incidence of nausea was great and claims made for this drug could not be substantiated.

3-4-bis(m-methyl-p-propionoxyphenyl)hexane (Meprane) is a synthetic compound more closely related to the diethylstilbestrol series than to the naturally derived estrogens. This material was used in doses not exceeding 3 mg. daily and completely relieved the symptoms of 81.5 per cent of patients treated. The incidence of nausea was relatively low, comparing well with Dienestrol in this regard. Lin<sup>19</sup> likewise noted this tolerance to the drug.

as costly as the most economical preparations used. Apart from cost, this material appears to have advantages over many of the oral estrogens. Ninety-five and eight tenths per cent of patients treated with 3.75 mg. or less daily obtained complete relief of symptoms. This satisfactory response has been noted by other workers.<sup>26, 27</sup> Progyon-DH is the only oral estrogen which produced less nausea and bleeding than Premarin. General tonic effects were noteworthy and the greatest percentage of patients who expressed clear-cut preferences for any drug designated Premarin. This estrogen appears to be moderately effective in promoting cornification of the atrophic vaginal smear.

### Symptomatic Response to Therapy

Response to therapy was frequently dramatic with disappearance of all symptoms occurring simultaneously. When relief was more gradual, certain symptom relationships were noted. Headaches appeared to remain more refractory to therapy than flushes and often required larger doses for complete relief. Alleviation of insomnia appeared to parallel closely relief of flushes. Although excellent response was noted in many cases, nervousness and depression were the most resistant of all symptoms to therapy. The administration of larger doses of drugs to effect control of these symptoms was not attempted. Vague bone and joint pains, paresthesias and other miscellaneous symptoms were often relieved with adequate doses of medication.

Certain patients, whose symptoms appeared to be adequately controlled, complained of return of headaches and/or flushes at regular intervals. Questioning revealed that these episodes corresponded with the times of the expected menses. This phenomenon occurred in patients who had had panhysterectomies and in whom the presence of ovarian tissue was most unlikely. Increasing the dose of estrogen usually suppressed these cycles. This periodicity obviously cannot be ascribed to the ovary in these patients and some other explanation must be considered. In this connection, the possible roles of the adrenal and the pituitary come to mind. The rhythmic increase in pain and nodularity in the breasts of some untreated oophorectomized women is also of interest.

Every patient could be completely relieved of her menopausal symptoms by one or another of the oral preparations administered.

### Vaginal Smears

In this series of two hundred patients, no smears were found which were positive for cancer. Two were considered suspicious but investigation with dilatation, curettage, and cervical biopsy revealed an endometrial polyp in one case, whereas no pathology could be demonstrated in the second. When smears were atrophic, primitive and even bizarre cells were occasionally observed. The administration of estrogen always eliminated doubt as to the character of these cells.

Failure to find genital cancer in this group of two hundred menopausal women may be attributed to the fact that periodic examinations and prophylactic therapy of precancerous lesions of the pelvic organs are routine. All patients must be given clearance by the Gynecological Department before they are referred to the Endocrine Department for therapy of their menopausal symptoms.

Because of variation in the production of estrogen by the ovaries of menstruating women, changes in the vaginal smear were not consistent with the type or amount of therapy; therefore, smears of amenorrheic patients only were used to interpret treatment responses.

Ephynal Acetate is an expensive preparation. Its role in the therapy of the menopause has still to be established. Its apparent freedom from toxicity makes it a potentially valuable agent for the treatment of the menopausal patient who bleeds easily with estrogens. It does not appear to act as a placebo since inadequate quantities of other drugs caused return of symptoms in patients who had been effectively controlled with Ephynal Acetate.

Estrone is a ketohydroxy estrin derived from urine, usually from the urine of pregnant mares. It is an excretory metabolic product of alpha-estradiol. In the majority of patients, 0.4 to 1.0 mg. each week was the effective maintenance dose. Bleeding occurred occasionally, but continuous therapy was often given over a period of many months. No other untoward effects were reported. Estrone is a moderately costly estrogenic preparation which is neither as effective nor as prolonged in action as alpha-estradiol benzoate.

Exact biological comparison of estrone and alpha-estradiol benzoate is difficult. This was recognized by The League of Nations Health Organization, and this Council recommended that biological units be abandoned and that relative potencies be discussed in milligrams. Clinically, one rat unit appears to be the equivalent of ten international units and relative doses of estrone and alpha-estradiol benzoate may usually be determined in this way. Patients differ so radically in their relative responses to these two materials, however, that one must not expect this ratio to hold in all instances.

Ethinyl estradiol (Estinyl) is a potent relative of alpha-estradiol with an ethinyl group on the 17-carbon atom of the phenanthrene nucleus. It is about five times as effective as parenteral alpha-estradiol but approximately 25 times more potent than oral alpha-estradiol.<sup>8</sup> It is the most potent estrogen available and it produces its pharmacological effects in smaller doses than any other drug known. It is one of the two most economical materials used in this study. Ease of administration was apparent in that 94.2 per cent of all patients were completely relieved. Ninety-six per cent of these required no more than 0.05 mg. daily for satisfactory maintenance.

Nausea was produced more frequently with this drug than with any other (9.4 per cent), and bleeding was a common complication. Nevertheless, when clear-cut subjective preference to any drug was voiced, Estinyl was more frequently preferred than any medication, excepting Premarin which led by a slight margin. Estrogenic effect on the vaginal smear was usually commensurate with improvement of symptoms. The economy of Estinyl, coupled with its ability to produce rapid relief of symptoms makes it a particularly useful medication for the routine therapy of the menopause.

Methylbisdehydrodoisynolic acid (methyl ester, dl-1-ethyl-2-methyl-7-hydroxy-1,2,3,4-tetrahydro-2-phenanthrene carboxylic acid) was used in doses of 0.05 to 2 mg. daily and gave complete relief to 40 per cent of patients treated. However, seven of the fourteen women relieved had mild pretreatment menopausal complaints. Its pharmacologic and biologic activity is similar to the previously discussed bisdehydrodoisynolic acid.

The high incidence of nausea (11.4 per cent) and the low therapeutic response are not in keeping with the reports of European investigators. The results with methylbisdehydrodoisynolic acid are, in general, similar to those observed with the demethylated form and together suggest that the usefulness of the materials may be less than originally believed.

Premarin (mixed conjugated estrogens) is derived from the urine of pregnant mares and contains a mixture of the excretory products of alpha-estradiol as well as small amounts of other estrogens of equine origin. Sodium estrone sulfate is the major component of this preparation. It is four times

5. Although hysterectomized women may be well controlled with oral medication, most of our patients preferred alpha-estradiol pellet implantation.

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All vaginal smears were taken and read by Dr. Mary B. Dratman.

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Control smears of patients with amenorrhea showed 24 per cent to be of the atrophic variety (Grade I, preponderance of basal or deep cells and abundant polymorphonuclear leucocytes); 45 per cent were of the moderately severe type (Grade II, deep cells, variable numbers of epithelial cells and polymorphonuclear leucocytes); 12 per cent showed slight estrogen deficiency (Grade III, predominance of noncornified epithelial elements, rare deep cells and occasional polymorphonuclear leucocytes); and 19 per cent showed full estrogen effect (Grade IV, with predominance of cornified cells, rare polymorphonuclear leucocytes and little mucus).

In general, flushes were of greatest intensity in patients with vaginal smears of Grades I and II and less prominent in Grades III and IV. Frequent exceptions were seen, however. Although the vaginal smear may be of occasional value in an equivocal case, its routine application for diagnosis and evaluation of therapy in the menopausal woman is unnecessary. It does, however, enable the physician to detect microscopic bleeding. In accordance with the experience of other investigators<sup>14, 19</sup> vaginal smear response to therapy in this series showed no necessary correlation with symptomatic relief. There appeared to be, however, more correlation between the clinical response and the vaginal smear than between the smear and the dose of medication employed.<sup>7</sup> After satisfactory relief of symptoms with any of the estrogens employed, a much greater increase in the dose was required to improve further the vaginal smear.

Analysis of the influence of each medication on the vaginal smear was performed in two ways. The relative effects of different medications in the same patient were compared with the average effects of various medications in different patients. These two methods of analysis showed fairly close agreement.

Estinyl, Dienestrol, and Meprane produced similar vaginal smear changes in the same patients and caused the same general range of response in different patients. In decreasing order of effect were Premarin, alpha-estradiol pellets, methylbisdehydrodisynolic acid and Ephynal Acetate.

### Summary

Two hundred women with a clinical diagnosis of the menopausal syndrome were studied. These women were treated with a variety of medications advocated for the therapy of the menopause. Response of symptoms and vaginal smears were determined. The incidence of undesirable effects was also noted. On the basis of these evaluations a comparison of the various medications used is presented.

### Conclusions

1. No single oral medication used in this study was universally effective in relieving menopausal complaints without the production of undesirable side effects.
2. It was possible, however, to relieve menopausal symptoms in all our patients by the oral administration of one or another of the preparations employed.
3. No deleterious effects may be anticipated as a consequence of estrogenic therapy providing the patient is under constant, careful supervision.
4. Although the vaginal smear may often be correlated with the symptom response, many exceptions exist and it appears to have little value for routine use. Occasional vaginal smears should be taken at intervals to detect microscopic bleeding.

1. *Morphine sulfate* grain 1/6 (.01 Gm.): The first dose was given when labor pains were strong and regular, or when the cervix was approximately 4 cm. dilated. Subsequent doses were given as necessary, but not more frequently than every three hours. One half of the dose was administered intravenously (grain 1/12 — .005 Gm.) and the rest subcutaneously, or all subcutaneously, depending upon the need for analgesia.

2. *Atropine sulfate* grain 1/100 (.6 mg.): This was given intravenously 10 to 15 minutes prior to expected delivery, principally to facilitate administration of the inhalation anesthesia.

3. *Anesthesia for delivery*: Nitrous oxide or cyclopropane was employed as needed. In the latter part of the series regional block anesthesia was employed to eliminate the respiratory depressant effect of inhalation anesthetics.

In order to obtain more data on the effects of morphine without supplemental inhalation anesthesia, forty-two patients were given morphine alone by the following schedule:

1. *Morphine sulfate* in doses of grain 1/8 (.0081 Gm.) was given intravenously when labor was definitely established and thereafter at the discretion of the obstetrician.

2. *Atropine* was given as before.

3. *Anesthesia for delivery*: As many women as possible were delivered under regional anesthesia.

The results obtained compared favorably with previous investigations carried out by Mengert in 1941.<sup>4</sup>

The second group included twenty patients who received morphine and Prostigmine according to the following schedule:

1. *Morphine sulfate* grain 1/6 (.01 Gm.): Given as in previous series.

2. *Prostigmine* (.5 mg.) intramuscularly: When labor was well established or cervical dilatation was approximately 4 cm., the total dose of morphine was repeated as necessary, but the Prostigmine was given not more often than every four hours.

3. *Atropine*: As before.

4. *Anesthesia for delivery*: Nitrous oxide and/or cyclopropane.

The dose of Prostigmine was limited because its effect upon the uterus is not known. However, there was no decrease in the average length of labor in this group. The analgesic effect of this combination was not materially different from that of the previous series. It was considered desirable to use this combination in view of Slaughter's<sup>5</sup> recent work indicating that the analgesic effect of morphine is enhanced by Prostigmine. He suggested that acetylcholine plays a part in the potentiation of the morphine effect. Results in this small series were not very conclusive.

The third group consisted of thirty-two patients in whom Methadon was used.

This drug is accredited with exceptionally good analgesic effects on experimental animals and it has been suggested as an agent which might have possibilities as an analgesic in obstetrics.<sup>6</sup> The first six patients were on the following schedule:

1. *Methadon* 5 mg. subcutaneously: The first dose was given as in previous schedules and repeated every 3 to 4 hours.

2. *Atropine sulfate* grain 1/100 (.6 mg.) also as before.

3. *Anesthesia for delivery*: As indicated.

This dosage was found to be inadequate and the initial dose was increased to 10 mg., followed by 5 mg. every 3 to 4 hours. Later, it was necessary to increase the dose to 10 mg., followed by 10 mg. every 1 to 2 hours because the

# A REPORT ON COMPARATIVE STUDIES OF NEWER DRUGS USED FOR OBSTETRICAL ANALGESIA

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THESE studies\* were undertaken to determine the clinical suitability of certain new analgesic drugs for pain relief during labor.

1, 3, dimethyl-4-phenyl-4-propionyloxy piperidine hydrochloride, Nisentil, a short-acting compound given the serial number Nu 1196 was the principal object of this investigation. The chemical synthesis and the pharmacologic action of this drug have been described by Ziering and Lee,<sup>1</sup> Holland and Gross,<sup>2</sup> and Randall and Lehmann.<sup>3</sup> Morphine, Methadon, and combinations of morphine with Prostigmine or scopolamine were also employed.

## Methods

The clinical estimation of analgesia during labor is difficult because of numerous variable factors. Consequently, all observations were made by one person in order to secure an evaluation largely devoid of the personal equation. As a control on the observations of this individual the reactions of the patient and of the attending obstetrician with regard to the effectiveness of the analgesia were considered. If these all agreed that labor pains were appreciably eased, the drug effect was considered good. Failure of the drug to produce the desired result was readily apparent, but evaluation of the effect as fair or indifferent was difficult. Patients vary widely in their tolerance to visceral and somatic pain. Many patients can be kept fairly comfortable during the first stage of labor with almost any available analgesic drugs, but during the expulsive phase of the second stage greater analgesia is required than can be given without jeopardizing the fetus. Consequently, it becomes necessary to administer supplementary anesthetic agents by inhalation or injection to keep the patient comfortable and permit whatever delivery procedures may be indicated. None of the results could be considered excellent because perfect analgesia was obtained only by the supplemental administration of gaseous anesthetics or the use of regional block, e.g., caudal and spinal anesthesia.

Records were kept on "Keysort" cards which facilitated the collection and comparison of data. The information thus obtained was then critically graded and tabulated on a large chart, significant portions of which are included in this report. Some selection of cases was employed early in the study, in that only essentially normal obstetric patients were used. Later, after no untoward effect of the drug had been noted, only those patients were excluded in whom the drug was not given as directed, or was given too late in labor to have any effect.

Observations were first made on the effects of morphine in order to establish a base line for comparison of the effects of the other drugs.

The first series studied included twelve patients receiving morphine sulfate according to the following schedule:

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approximately 41 per cent, had "good" analgesia. Fifty-two patients received Nu 1196 in 20 mg. or less doses subcutaneously. Twenty-one, or 40 per cent, had "good" analgesia. Sixty-seven patients received Nu 1196 in 30 mg. doses subcutaneously. Thirty patients, or approximately 45 per cent, had "good" analgesia. Oral Nu 1196 combined with subcutaneous dosage gives a lower percentage of "good" results, 5 patients out of twenty-four having "good" analgesia.

TABLE I

DRUG	NO. CASES	ANALGESIA		
		FAILURE	FAIR	GOOD
Morphine	54	8	36	10
Morphine and Prostigmine	20	0	17	3
Methadon	32	7	12	13
Nu 1196, 10-20 mg.	52	11	20	21
Nu 1196, 30 mg.	67	11	26	30
Nu 1196, oral and subcutaneous	24	7	12	5
Morphine and scopolamine	39	3	13	23
Nu 1196 and scopolamine	43	6	23	14

With any drug used in obstetrics, a factor probably of more concern than analgesia is the effect on the baby. In trying to evaluate these effects a number of other factors must be considered, such as antepartum and intrapartum complications, type of delivery, and anesthetics used. At the outset of this study, most deliveries were conducted under cyclopropane or nitrous oxide, or a combination of the two agents. Later, saddle block anesthesia was used more frequently. Therefore, for evaluating fetal depression, the patients have been divided into three groups: those delivered under regional or spinal anesthesia; those under inhalation anesthesia; and those under combinations of regional or spinal and inhalation.

Fetal depression was judged by the time of onset of spontaneous breathing, the degree of cyanosis, muscle tone, time required for revival of depressed babies, and methods employed for resuscitation (Table II). In final evaluation of the drugs, the time up to the onset of spontaneous breathing and the time required for resuscitation have been most significant.

Revival time was considered as that required to initiate good crying or breathing to the point where it was felt safe to leave the infant. Some babies who cried immediately became apneic later and took longer to arouse. Table II shows the various analgesic drugs and indicates the degree of respiratory depression of the fetus obtained in each group.

In the entire group there was a total of 324 mothers and 330 infants (including six sets of twins). One hundred eighty-six mothers (192 infants) received Nu 1196 either alone or with scopolamine. One hundred forty-three mothers received Nu 1196 alone.

Antepartum complications included three patients with hypertension, three with diabetes mellitus, five with pre-eclampsia, one in premature labor, one with chronic nephritis, one with syphilis, one with a congenital heart lesion (intraventricular septal defect), one with Friedreich's ataxia and one with a contracted pelvis.

Intrapartum complications included eight cases of prolonged labor. Three patients had retained placentas and resultant hemorrhages of over 600 c.c. These complications were scattered through the various groups and appeared to have no relation to the drugs used. The drugs did not tend to aggravate existing complications.

desired degree of analgesia was not obtained. Because of the poor analgesia and the prolongation of respiratory depression of the newborn, even with small doses, this drug was considered unsatisfactory for obstetric analgesia and the series was discontinued.

Nu 1196 was first used under the following schedule:

1. *Nu 1196* 10 mg. subcutaneously: The first dose was given when the patient was definitely in labor or when cervical dilation had reached approximately 4 cm. Subsequent doses were injected at one-hour intervals, as necessary. The final dose was not to be given during the last hour before delivery.

2. *Atropine*: As before.

3. *Anesthesia for delivery*: Regional or spinal anesthesia is preferred to inhalation agents, whenever feasible.

Because of the limited analgesic effect of 10 mg. of Nu 1196 the dose was gradually increased until 30 mg. every hour were given. At first an attempt was made to omit the administration of the drug within the last hour before delivery. Later, however, this precaution was abandoned in order to ascertain the time after an injection when the respiratory depressant action is most marked.

Nu 1196 was also given orally according to the following schedule:

1. *Nu 1196* 30 mg. orally, 15 mg. subcutaneously: The oral dose was given only to those patients from whom food had been withheld for several hours and who were definitely in labor. The 15 mg. subcutaneous doses were started at the same time or later, and were repeated every hour as necessary.

2. *Atropine*: As before.

3. *Anesthesia for delivery*: Saddle blocks were preferred, but regional or inhalation anesthesia was used occasionally.

The dose was later increased to 40 mg. orally and 20 mg. subcutaneously.

Nu 1196 was also given in 20 mg. doses with scopolamine in doses of 1/150 grains (.432 mg.) repeated two to three times to produce amnesia, at the discretion of the obstetrician. Nu 1196 was given at the same time or more often.

In the morphine-scopolamine group the patients received morphine and scopolamine in a similar manner.

## Results and Discussion

Side reactions were not severe in any group and were confined largely to nausea and emesis. Patients receiving Methadon occasionally complained of tingling in the area in which the drug was given. Nu 1196 seemed to have moderate hypnotic power while Methadon appeared to have none.

Analgesia was rated as indicated in Table I for the various drugs which are grouped alone or in combinations, and in some cases according to the amount and manner of administration.

As stated earlier, it was most difficult to be dogmatic about the degree of analgesia except in those cases designated "good." Accordingly, in interpretation of the results, the number of "good" cases is the significant factor. In those who received scopolamine the factor of amnesia made the determination of analgesia almost impossible and certainly unreliable.

Patients who received morphine and morphine-Prostigmine had the lowest percentage of "good" analgesia. Of the fifty-four patients receiving morphine, ten, or approximately 19 per cent, had "good" analgesia. Twenty patients received morphine and Prostigmine. Three, or approximately 15 per cent, had "good" analgesia. Of the thirty-two patients receiving Methadon, thirteen, or

In Table II indicating fetal depression, patients are grouped according to the type of anesthesia used for delivery. However, with certain drugs, all the mothers were delivered under inhalation anesthesia and had to be compared with similar groups.

Among the seven patients who received Methadon and were delivered under regional anesthesia, five babies cried within the first 15 seconds, but two were secondarily depressed and required more than one minute of stimulation to initiate good crying.

As indicated earlier, this drug was discontinued because respiratory depression increased greatly as dosage was augmented.

Of the eighteen patients given morphine and delivered under regional anesthesia, ten, or 56 per cent, of the babies cried within the first 15 seconds; three, or 17 per cent, were depressed and required more than one minute of stimulation.

Of the fourteen patients given Nu 1196 in 20 mg. or smaller doses who delivered under regional anesthesia, eleven, or 79 per cent, of the babies cried within the first 15 seconds, and two, or 14 per cent, were depressed, i.e., required more than one minute of stimulation to initiate good crying and breathing. Of the thirty-eight babies of patients who received 30 mg. of Nu 1196 and delivered under regional anesthesia, twenty-five, or 66 per cent, cried within the first 15 seconds, and six, or 16 per cent, required more than one minute of stimulation to initiate good crying and breathing.

Adding scopolamine to Nu 1196 appeared to increase the tendency to apnea in the babies of the twelve patients delivered under regional anesthesia. Only six of the babies cried within the first 15 seconds and two showed some degree of respiratory depression.

In patients receiving Nu 1196 orally and subcutaneously, there were no cases delivered under regional anesthesia alone, but fifteen were delivered under inhalation anesthesia and four of the babies were depressed. Among the nine women delivered with regional-inhalation combination three babies were depressed. Whether this depression was due to the anesthetic or the longer action of the analgesic drug given orally is not known.

In thirty-two patients who received morphine and scopolamine and delivered under inhalation anesthesia, sixteen of the babies cried within the first 15 seconds; fourteen were depressed and required more than one minute of stimulation to initiate good breathing and crying.

In twenty-three patients who received morphine alone and delivered under inhalation anesthesia, thirteen of the babies cried within the first 15 seconds; eleven of the babies were depressed.

Twenty patients received morphine and Prostigmine and delivered under gas anesthesia. In this group seventeen of the babies cried within the first 15 seconds while 5 were depressed.

These results are summarized in Table III.

In some of the groups delivered under regional anesthesia an attempt was made to correlate the fetal depression with time of administration of the drug. The results are shown in Table IV.

In those cases marked with an asterisk on the chart there were other significant factors, e.g., one baby delivered by breech extraction and the other by difficult low forceps, which more likely caused the depression than the drug administered. With Methadon the depressions occurred when the drug was administered 3 to 4 hours before delivery. With morphine, the depression appeared to occur during the 31 to 240 minute period after administration. Nu

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TABLE II

AGENT		NUMBER CASES	ANESTHESIA	SPONTANEOUS BREATHING				REVIVED (CRYING) AFTER					TOTAL NUMBER DE-PRESSED					
				1-15 SEC.	16-30 SEC.	31-60 SEC.	60 SEC.	1 MIN.	2 MIN.	3 MIN.	4 MIN.	5 MIN.		10 MIN.	15 MIN.			
Methadon		7	Regional	5		2	2											
Methadon		16	Inhalation	12		2	3		3									
Methadon		9	Regional + inhalation	4	2	2												
Morphine and Prostigmine		20	Inhalation	17	2			1	1									
Morphine		18	Regional	10	3	4	1											
Morphine		23	Inhalation	13	3	4	3											
Morphine		13	Regional + inhalation	6	1	1	5											
Morphine and scopolamine		32m	Inhalation	16	4	9	4	1	1									
Nu 1196 and scopolamine		33b	Regional	6	2	4												
Nu 1196 and scopolamine		12	Inhalation	6	2	4												
Nu 1196 and scopolamine		21	Regional	10	4	2	5											
Nu 1196 10-20 mg.		10	Inhalation	5	2	2	1											
Nu 1196 10-20 mg.		32m	Regional + inhalation	16	8	5												
Nu 1196 10-20 mg.		33b	Inhalation	3	1	1	1											
Nu 1196 30 mg.		6	Regional	11	2													
Nu 1196 30 mg.		14	Regional + regional	25	4	5	4											
Nu 1196 30 mg.		37m	Inhalation	10	2													
Nu 1196 30 mg.		38b	Regional + inhalation	12	1	2	1											
Nu 1196 30 mg.		14b*	Inhalation	10	1	4	1											
Nu 1196 30 mg.		15m	Regional + inhalation	8														
Nu 1196 oral		15m	Inhalation	21	2	7												
Nu 1196 oral		16b	Regional + inhalation	29	7	9	1											
Methadon		9	All types	30	11	6	1											
Morphine		32	All types	47	7	7	1	3	1	4	3	1	1	1	1	1	1	14
Nu 1196 10-20 mg.		54	All types															
Nu 1196 30 mg.		52m	All types															
Nu 1196 30 mg.		53b	All types															
Nu 1196 30 mg.		67m	All types															
Nu 1196 30 mg.		69b	All types															

m = mothers  
b = babies  
\*Excluding one stillborn anencephalic monster.

m = mothers  
b = babies

\*Excluding one stillborn anencephalic monster.

began to breathe and cry immediately after birth and appeared to be in excellent condition when transferred to the nursery. Twelve hours after birth it was found dead. Autopsy findings showed aspiration and acute asphyxia.

### Summary

1. Nu 1196 (Nisentil) was given subcutaneously in 30 mg. or smaller doses to one hundred eighty-six patients. It compared favorably in analgesia with any of the other drugs employed. Greater flexibility in repeated administration of the drug was possible because of its short action.

2. Administered orally, Nu 1196 (Nisentil) did not seem to prolong or enhance the degree of analgesia. Its effect was not as great as when given parenterally. Nu 1196 with scopolamine was given to forty-three mothers. Fetal depression in this group was greater than when the drug was used alone.

3. Nu 1196 (Nisentil) appeared to have a moderate hypnotic effect on the mothers and produced somewhat less fetal depression than any of the other drugs used. Depression seemed most likely to occur in the 31 to 120 minute period after administration. There were no ante- or neonatal deaths attributable to the drug.

4. Morphine used alone in the amounts stated gave less analgesia than Nu 1196. There was no appreciable difference in analgesia when Prostigmine was added to morphine.

5. Methadon in larger doses gave nearly the same degree of analgesia as Nu 1196 but when given in larger doses there was marked fetal depression. Its use was therefore discontinued.

6. Side effects were minimal with all drugs. Nausea and emesis were most prominent. A few patients receiving Methadon complained of tingling at the area of injection.

7. There was no increase in the incidence of operative deliveries attributable to Nu 1196.

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1196 in doses of 20 mg. or less caused no significant depression. With Nu 1196 in 30 mg. doses, the depression appeared to occur in the 31 to 120 minute period after administration with the largest number in the 31 to 60 minute period.

TABLE III

DRUG	TYPE ANESTHESIA	NO. CASES	SPONTANEOUS BREATHING	
			1-15 SECONDS	DEPRESSED
Nu 1196 10-20 mg.	Regional	14	11	2
Nu 1196 30 mg.	Regional	38	25	6
Nu 1196 and scopola- mine	Regional	12	6	4
Methadon	Regional	7	5	2
Morphine	Regional	18	10	3
Morphine and sco- polamine	Inhalation	32 Mothers 33 Babies	16	14
Morphine	Inhalation	23	13	11
Morphine and Pro- stigmine	Inhalation	20	17	5
Nu 1196 and scopola- mine	Inhalation	21	10	10
Nu 1196 and scopola- mine	Inhalation and regional	10	5	3
Summary of Methadon	All types	32	21	11
Summary of morphine	All types	54	29	19
Summary Nu 1196 10-20 mg.	All types	52	30	11
Summary Nu 1196 30 mg.	All types	67 Mothers 69 Babies	47	14

TABLE IV

DRUG		NO. CASES	TIME INTERVAL BEFORE DELIVERY (MINUTES)					240 PLUS
			0-30	31-60	61-120	121-180	181-240	
Methadon	Mothers	7	0	0	3	0	3	1
	Depressed Babies						2	1
Morphine	Mothers	18	1	4	5	6	1	1
	Depressed Babies		0	2	1			
Nu 1196 10-20 mg.	Mothers	14	1	1	4	4	3	1
	Depressed Babies				1*			1*
Nu 1196 30 mg.	Mothers	37	0	15	14	5	1	2
	Depressed Babies		0	4	2			

\*Significant factors discussed above.

Average lengths of labor did not appear to be influenced by any of the drugs used. The incidence of operative deliveries increased with the use of regional block anesthesia and was comparable in each series of analgesic drugs used.

Except for the neonatal mortality among definitely premature babies and monsters, there was one death possibly attributable to the analgesic agent. This occurred in a baby whose mother received morphine. The baby was of good size,

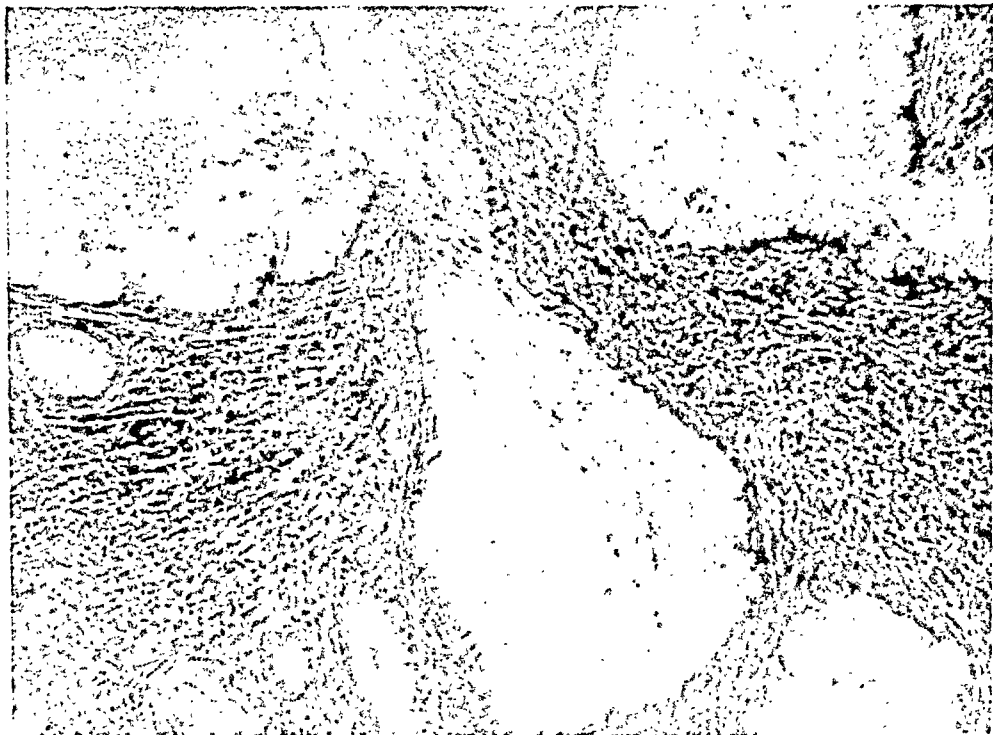


Fig. 1.—Cervical biopsy, May 12, 1947. Note the profusion of functioning cervical glands and the inflammatory reaction.

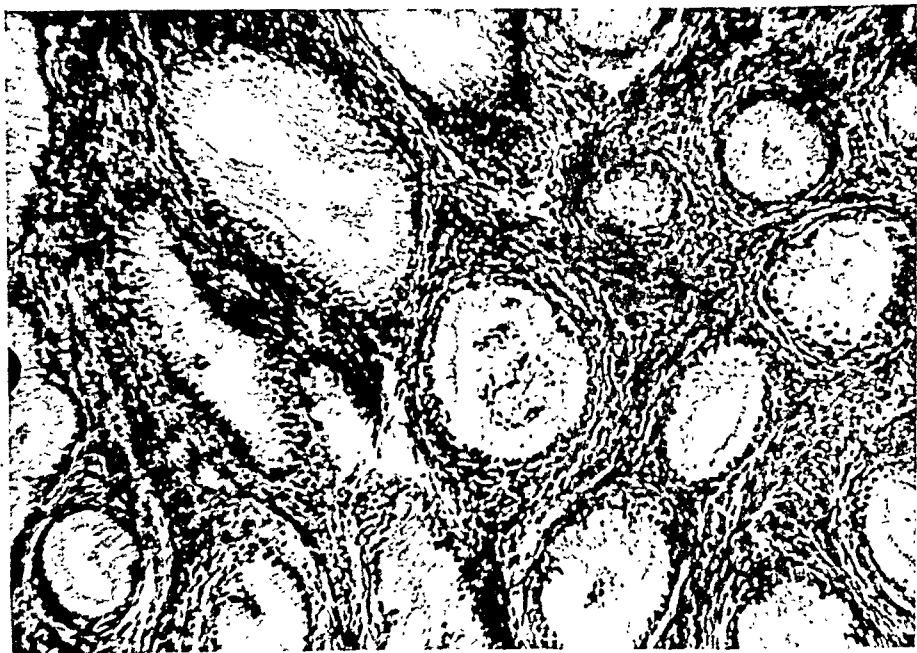


Fig. 2.—Operative specimen (cervix). Note similarity in appearance to Fig. 1.

## DIFFUSE ADENOSIS: A RARE INVASIVE LESION OF THE UTERUS

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THE purpose of this paper is to present a condition, the nature of which has not been satisfactorily explained in terms of any of the familiar processes known to occur in the cervix and uterus. The authors have been unable to find a reference in the literature to any condition similar to that which is about to be described.

The term "diffuse adenosis" was chosen to describe a unique process affecting the entire uterus, cervix, and parametrium, and characterized by the presence of innumerable mucus-secreting glands in the affected tissues. In the selection of this term there is no intended implication as to the exact nature of the condition; however, the resemblance of the infiltrations to true cervical glands is apparent. In view of the course of the case under consideration, it would seem likely that this condition had its origin in the cervical glands, since the disease had apparently been present in the cervix for several months. This observation would immediately raise the question of a malignancy arising in the cervical glands.

The probability of this condition representing a form of invasive carcinoma certainly cannot be denied since the evidence of invasion is unequivocal, although the cytological evidences of malignancy are not striking. In any case, carcinoma of this type has not been encountered in the authors' experience.

It has been stated by Te Linde in the chapter on endometriosis in his textbook, *Operative Gynecology* that excessive growth and invasiveness without malignant characteristics are limited in the human being to the glandular and stromal elements of the endometrium. If the condition under discussion could be considered nonmalignant, a comparison to adenomyosis might be justified.

A condition of the sort described above occurred in a 44-year-old woman who was first seen on the Gynecology Service in May, 1947, at which time she complained of excessive vaginal bleeding with pain in the left side and back. The previous menstrual history was that of regular periods occurring every twenty-eight to thirty-one days, lasting eight days. She had had thirteen living children and three abortions. The physical examination revealed a chronically ill woman, about 45 years of age, who showed slight elevation of the blood pressure, a temperature of 99.4° F., and a pulse rate of 80. The uterus was enlarged to twice its normal size and was freely movable. The cervix was greatly enlarged and bled freely on manipula-



The cleftlike spaces were present in the myometrium and fundus, the lower uterine segment, and the stroma of the cervix. Both tubes showed subserosal hemorrhages. The right tube measured approximately 110 mm. in length and 5 mm. in diameter in the proximal portion and 43 mm. in the distal portion. The left tube showed similar characteristics. They sectioned with moderate ease, showing some thickening of the wall. The ovaries averaged 30 mm. in greatest dimension and sectioned with moderate ease displaying hemorrhagic follicles and a corpus luteum.



Fig. 4.

Fig. 4.—Operative specimen. Myometrium showing cystic space lined by mucus-type cylindrical epithelium. These were encountered throughout the myometrium. (See Fig. 7.)



Fig. 5.

Fig. 5.—Operative specimen. Parametrium. Note presence of glandular elements and fat cells in upper left.

*Microscopic Findings.*—Section through the cervix showed rather marked coagulation necrosis of the covering epithelium, much of which was desquamated. The fibromuscular stroma was diffusely infiltrated with innumerable regular-appearing cervical glands showing marked secretory activity. The nuclei were small and uniform appearing. The glands had essentially the same appearance in all portions of the section. The remainder of the stroma was infiltrated with round cells. Section through the uterus showed a moderately atrophic endometrium and typical glands which showed no evidence of secretory activity. The stroma showed considerable tendency to fibrous metaplasia. Other sections showed in addition to the usual endometrial glands, atypical slightly irregular glands showing much secretory activity. The cytoplasm of the cells contained secretory vacuoles and the glands bore a resemblance to ordinary cervical glands. The myometrium also showed diffuse scatterings of similar mucus-secreting glands still bearing a striking resemblance to cervical glands. Most of the

tion. The laboratory examination was negative except for a red blood count of 3.3 million with 10.1 Gm. of hemoglobin and 10,700 white blood cells.

A dilatation and curettage, performed a few days after admission to the hospital, resulted in a pathological diagnosis of acute and chronic cystic cervicitis, the endometrial scrapings apparently being indistinguishable histologically from the cervical biopsy.

During the months of June and July the patient was readmitted and treated on three different occasions and at each time cervical biopsies revealed an acute and chronic cervicitis with numerous mucus-secreting glands present in the cervical fragments.



Fig. 3.—Operative specimen. Endometrium showing both typical proliferative endometrial glands and the aberrant mucus-type glands. Compare with Fig. 2.

On November 3 the patient was readmitted for the fourth time with the same complaints. During this admission a bilateral salpingo-oophorectomy and total hysterectomy were performed. At operation there appeared to be a chronic indurative process involving the anterior uterine wall, and the bladder floor, the parametrium, and the vaginal cuff. In the parametrium, especially between the uterus and bladder, and extending to each wall of the pelvis, yellowish plaques were noted which exuded a gelatinous material on section. Post-operative recovery was uneventful and the patient was dismissed on November 18.

Complete description of organs and tissues removed was as follows:

*Gross Description.*—The specimen consisted of a uterus including the cervix, both tubes, and ovaries (Fig. 7). The uterus including cervix measured 110 by 90 by 50 mm. The cervical os was patent. The surface was pinkish gray in color with a granular appearance. The endometrial cavity contained a large blood clot. The endometrium measured about 1 mm. in thickness. The myometrium showed asymmetrical thickening measuring from 22 to 30 mm. in thickness. The cut surface of the myometrium had a whorled fibrous appearance and there were numerous irregular cleftlike spaces seen, varying in size from 1 to 6 mm. in greatest dimension. Most of these contained gelatinous material and a few contained a small amount of blood.



Fig. 7.—Operative specimen. See text for description.

### Discussion

In the management of this case, two points should be considered. Hysterectomy was delayed because of the very evident infection of the cervix, which was partially controlled by local measures, antibiotics, and an electroconization. Perhaps irradiation therapy should have been given sooner, but the uncertain nature of the condition and the general well-being of the patient delayed this measure until there was proved malignancy.

The subsequent development of the squamous-cell carcinoma in the vaginal vault presented a complicating factor in the management of this case, and, presumably, should be regarded as independent of the adenomatous lesions. The likelihood of its origin from the vaginal mucous membrane is strengthened by the fact that other sites of origin have been ruled out.

### Summary

1. A case of an atypical invasive glandular lesion of cervix and uterus was presented.
2. Discussion of the clinical management was given.

### Reference

Te Linde, Richard W.: Operative Gynecology, Philadelphia, 1946, J. B. Lippincott Company, Chapter 22.

glands were lined with regular cells showing no nuclear changes. A few areas showed pleomorphic cells and there were very rare mitotic figures. In no case, however, was nuclear stratification observed. Some of the myometrium showed the glands to be widely dilated and cystic, containing large amounts of mucoid material and showing atrophy and desquamation of the lining epithelium. Section through the parametrium showed a few glands within the fibrous tissue. These glands had the typical appearance of cervical glands and showed the usual cytological abnormalities. In many of the glands throughout the uterus, the secreting portions of the cells were extremely tall and had the appearance of goblet cells. Section through the ovary showed a few corpora fibrosa and thickening of the arterial walls. Section through the uterine tube showed some fusion of the mucosal folds and thickening of the wall. There were occasional foci of round cell infiltration.

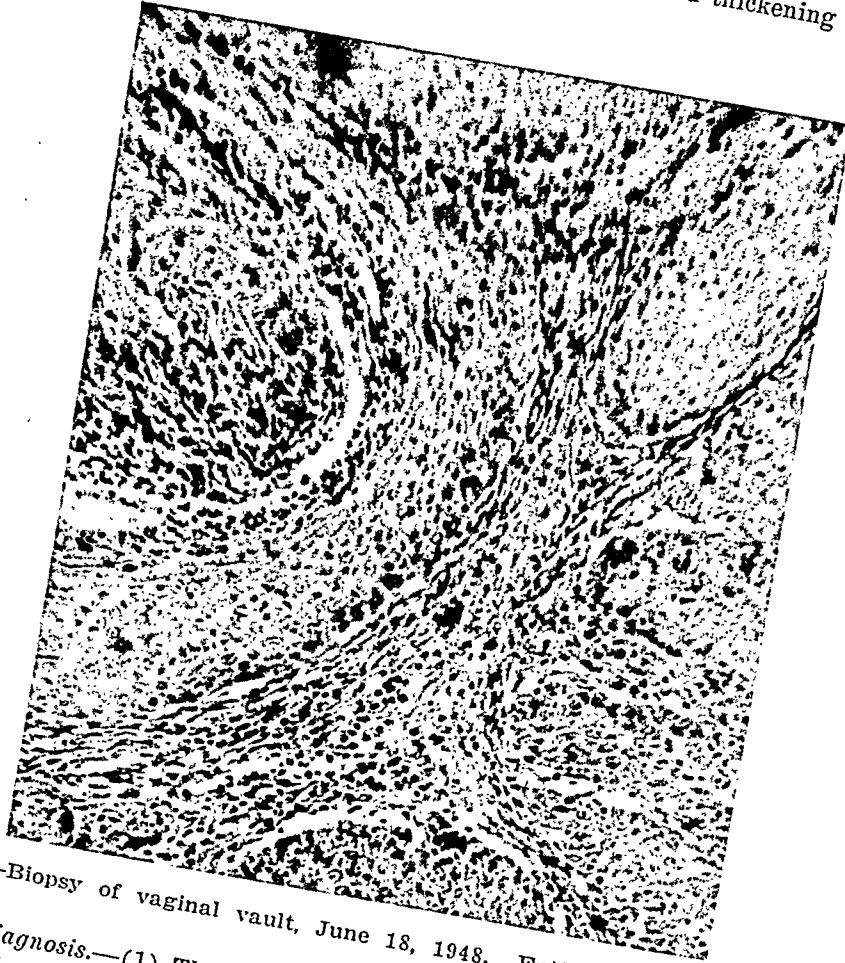


Fig. 6.—Biopsy of vaginal vault, June 18, 1948. Epidermoid carcinoma.

*Pathologic Diagnosis.*—(1) The lesion probably represents an atypical low-grade mucoid type of adenocarcinoma. Note: the cytologic characteristics of a malignant lesion are largely lacking. However, there is definite invasion. The origin of the lesion is quite obscure. (2) Chronic salpingitis.

The patient returned again on February 6 by request of the follow-up service, at which time she was complaining of painful urination. A mass was noted at the apex of the vagina and involving the floor of the bladder. The vaginal walls appeared well healed. Cystoscopic examination showed some frondlike growths in the bladder. These were biopsied and reported as chronic cystitis.

She was next seen on June 18, again by request, at which time she had no complaints. Pelvic examination showed the same mass above the vagina and now an ulceration of the vaginal vault. This was biopsied and was reported as Grade III, squamous-cell carcinoma. At this time the patient was referred to the radiologist for roentgen therapy.

from a situation in which the rate of loss through the dural puncture is greater than the rate of restoration by the choroid plexus. The rate of leakage depends chiefly on the size of the puncture and the time at which the patient assumes the upright position. The rate of re-formation of spinal fluid is dependent on the tonicity and volume of water in the blood and interstitial spaces. Water which is free to influence the formation and absorption of cerebrospinal fluid (which we term "free water" for convenience) is water that is in excess of the prior demands for water made by the more vital functions of temperature regulation, maintenance of blood volume, urine formation, and pulmonary respiration. Water that is hypotonic is more effective in increasing the volume of cerebrospinal fluid. A large percentage of postpartum patients do not have a volume of hypotonic water available in sufficient quantity to maintain the new formation of cerebrospinal fluid at a rate which can compensate for a relatively large loss by leakage. "Free water" is probably markedly reduced in these patients by the less than normal intake of fluid and food during labor and the first few days of the puerperium coupled with the larger than normal losses of water during the same period. The fluid output is larger than normal because of the increased elimination of water with sodium salts that results from the hormonal changes of the puerperium and because of the considerable blood loss during the third stage of labor and the postpartum flow of lochia rubra.

### Methods

These facts have justified the trial of two possible means of reducing the incidence of postspinal headache:

1. To decrease the rate of loss of cerebrospinal fluid by minimizing the size of the lumbar puncture wound.
2. To increase the rate of formation of cerebrospinal fluid by enlarging the volume of "free water" in the postpartum patient.

1. The size of the dural opening may be decreased by attention to several details regarding the needle and the technique of lumbar puncture but the primary factor is the diameter of the spinal needle. We therefore tried a 24 gauge spinal needle. Lumbar puncture with a 24 gauge spinal needle requires the aid of a double needle\* system (a needle within a needle) because of the great flexibility of the long 24 gauge needle. The principle of the double needle originated with Hoyt in 1922.<sup>3</sup> In the United States there has been no double needle commercially available since the Hoyt needle was discontinued for lack of general acceptance.<sup>4</sup> The outer needle is a 20 gauge, 7.5 cm. spinal needle. The inner needle is 24 gauge, 10 cm. which accurately fits the outer needle. Each of the two needles have their own stylets.

The 24 gauge needle allows spinal fluid to flow so slowly that, for speed and convenience, the anesthetic drug should be in solution, e.g., Pontocaine, Metycaine, or Nupercaine. The 20 gauge needle, with its stylet in place, is introduced through the anesthetized skin wheal and subcutaneous area to the interspinous ligament or ligamentum flavum. A resistance greater than subcutaneous tissue is felt at this depth, where the point of the needle is within 1 cm. of the dura. The stylet is removed and the 24 gauge needle, with its own stylet in place, is then passed through the lumen of the 20 gauge needle into the subarachnoid space. In early trials the tendency is either to push the 20 gauge needle too far so as to puncture the dura or to stop at a point short of the ligament. If the 20 gauge needle is in correct position the puncture of the dura by the inner 24 gauge needle is easily and gently ac-

\*The double needle which we have been using is that suggested by Mr. Oscar Schwidetzky of Becton, Dickinson and Company in response to our inquiry.

# THE PREVENTION OF HEADACHE AFTER SPINAL ANALGESIA FOR VAGINAL DELIVERY BY THE USE OF HYDRATION AND A 24 GAUGE NEEDLE

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THE postspinal headache is a serious objection to the use of spinal analgesia in obstetrics. Before we devoted extra attention to avoiding it, our obstetricians were reluctant to have their patients receive spinal analgesia.

## Incidence

The incidence of this complication in several reports of spinal anesthesia for vaginal delivery has varied from 20 per cent<sup>1</sup> to zero.<sup>2</sup> Most observers find it too frequent to be disregarded. These apparently conflicting experiences are confusing unless the problem of postspinal headache is understood as depending on a large number of subtle factors which may influence the observed incidence of headache.

The apparently greater importance of the postspinal headache problem in our service is attributable to the following factors:

- a. The majority of our patients are up and out of bed on the first or second postpartum day.
- b. Ours are largely private cases and the patients do not hesitate to voice their complaints.
- c. The patients are chiefly of the Mediterranean and Semitic peoples whose threshold for the perception or complaint of pain is lower than that of the Negro, Asiatic, and Scandinavian groups.
- d. Postspinal headaches in our patients are carefully sought and reported. The complaint, however, is never solicited of the patient.

These factors are variables which prevent comparison with any series of cases reported by others, even when the technique of spinal anesthesia has been identical. We have, therefore, controlled our results by our own earlier experience with the same group of obstetricians and the same types of patients.

## Pathogenesis

We began this study in February, 1947. Out of many diverse and conflicting statements in more than one hundred articles, we formulated the following as a working basis. The common type of postspinal headache is due to leakage of spinal fluid through the persisting opening in the dura with the consequent development of a subnormal volume and pressure of cerebrospinal fluid. This, in turn, leads to dilatation of intracranial veins and, in the upright position, to traction on the anchoring structures of the brain, the stimuli directly causative of headache. The subnormal volume of spinal fluid results

tically significant in view of the mathematical finding that this difference is larger than three times the standard error of the difference.<sup>6</sup> This result is especially remarkable when it is realized that even a single complaint of headache on one day sufficed to bring the patient to our attention and record. Furthermore, the 24 gauge series was done by anesthetists learning to use the 24 gauge needle. We suspect that the single severe headache in the 24 gauge series was the result of an inadvertent puncture with the 20 gauge portion of the "double needle." We now test every "double needle" puncture for an accidental puncture with the 20 gauge needle by withdrawing the 24 gauge needle before removing the 20 gauge needle. A 20 gauge needle puncture is quite likely to be followed by a moderate or severe headache in our experience with postpartum patients. Seven patients were deliberately punctured with a 20 gauge needle; four developed headache; two suffered to a severe degree. We were unable to continue the 20 gauge series to obtain the number of cases required for statistically significant results.

The following observations on the incidence of headache after spinal anesthesia for cesarean section confirm the importance of the gauge of spinal needle:

TABLE II. PERCENTAGE OF HEADACHES IN CESAREAN SECTION

	NO. OF PATIENTS	MILD	MODERATE	SEVERE	TOTAL
16 Gauge needle (with ureteral catheter for continuous spinal anesthesia)	26	15	0	27	42
20 Gauge needle	32	18.7	0	0	18.7
22 Gauge needle	26	3.8	3.8	0	7.7

These groups show a decrease in headache incidence with each reduction in size of needle diameter. In spite of the small number of cases, there is tested statistical significance in the difference between the 16 gauge and the 22 gauge series. Especially noteworthy is the comparative incidence of headaches of severe degree.

We have tried to determine the value of hydration by the following two series:

TABLE III. PERCENTAGE OF HEADACHES IN VAGINAL DELIVERIES

	NO. OF PATIENTS	MILD	MARKED	SEVERE	TOTAL
22 Gauge needle without Pituitrin and water	93	8	12	6	26
22 Gauge needle with Pituitrin and water	108	6.5	2.8	0.9	10

These two series differed only with respect to the special effort to increase hydration in one group by the use of Pituitrin and encouraged drinking of water. Patients were not informed of the reason for these orders.

The incidence of 26 per cent in the 22 gauge series without hydration was decreased to 10 per cent in the 22 gauge series with hydration, a difference of verified statistical significance.<sup>6</sup> Of equal importance is the fact that the headaches in the latter group were largely of the mild variety. Further evidence of the value of forced hydration, although not conclusive in itself, is our experience with three cases accidentally punctured with the 20 gauge outer needle in our early trial of the double needle system. These three cases were given Pituitrin and water to prevent the expected headache. One headache occurred and that one was very mild, a single complaint for only one day.

complished. When the inner needle readily passes beyond the point of the outer needle, it is most probable that the former is in the subarachnoid space. The spinal fluid comes out so slowly that one should wait and watch the hub of the needle for a few seconds. If fluid does not come, the stylet of the 24 gauge needle is reinserted and the two needles are pushed on as one unit until the projecting inner needle is felt to pierce the dura.

2. The volume of "free water" is increased by encouraging water drinking during and after labor. Ten glasses of fluids are ordered for each of the first two days after delivery. When dehydration or blood loss is greater than usual, the patient receives one or more infusions during or after labor, as a rule, 1 L. of 5 to 10 per cent glucose in distilled water, administered slowly. Normal saline is less effective than distilled water with glucose. As an aid in retaining "free water" in the body, we utilize the antidiuretic property of whole posterior pituitary extract. The dosage is 10 units of posterior pituitary extract (1 c.c. of obstetrical Pituitrin) injected hypodermically every 12 hours for three doses. Posterior pituitary extract increases reabsorption of water by the renal tubular cells while allowing a disproportionately larger excretion of sodium ions.<sup>5</sup>

No breast difficulties have been observed despite the large proportion of our patients who do not nurse their infants. This is due in part probably to the prophylactic use of estrogenic drugs.

### Headache, Diagnosis and Classification

Residents and obstetricians were encouraged to cooperate in recording and reporting all headaches, although little effort was needed in this direction with most of our staff. Where an obstetrician or patient is aware of the fact that a spinal puncture has been performed, there is a tendency for either of them to attribute any headache to the lumbar tap. It is therefore necessary that the criteria of a true postspinal headache be used in the diagnosis of a headache. A headache was judged to be of spinal origin when it was aggravated by sitting up and relieved by lying down. A headache was counted even if it was complained of only once or lasted one day, in which case it was classified as "mild"; if it was present on more than one day it was considered to be "moderate"; if it prevented the patient from getting out of bed or persisted for five days it was "severe."

### Results

We have attempted to evaluate the influence of the size of the needle by the following two series:

TABLE I. PERCENTAGE OF HEADACHES

	NO. OF PATIENTS	MILD	MODERATE	SEVERE	TOTAL
22 Gauge needle without Pituitrin and water	93	8	12	6	26
24 Gauge needle without Pituitrin and water	120	0.8	0.8	0.8	2.5

These two series of vaginal deliveries were anesthetized by the same personnel; all received Nupercaine and glucose intraspinally; all were accorded routine postpartum care and observation; none received any special prophylactic measure against headache.

The incidence of 26 per cent in the 22 gauge series was reduced to 2.5 per cent in the 24 gauge series. The difference between the two series is statis-



followed by a headache. A patient punctured with a 16 gauge needle may be less likely to suffer a headache than one punctured with a 20 gauge needle contrary to expectation according to the leakage theory, if the former is favored by secondary factors which influence the complaint of postspinal headache. These secondary factors are:

- a. The duration of horizontal position after puncture;
- b. the threshold for pain and readiness to complain;
- c. the presence of stimuli which distract attention from headache;
- d. the coincidental use of analgesics for wound pain, and, finally, but most important,
- e. the state of hydration.

The value of administering parenteral fluids has been repeatedly reported.<sup>13-16</sup> The relationship between the state of hydration and the susceptibility to postspinal headache, however, has been emphasized only by Masserman.<sup>9</sup> The varying degrees of hydration among apparently normally hydrated patients seem to us to be an essential but overlooked factor in the seemingly unpredictable incidence of a postspinal headache. Solomon<sup>14</sup> measured lumbar spinal fluid pressure at varying intervals after lumbar puncture in a series of psychiatric patients. Many showed a persistently subnormal pressure; others, however, rapidly and spontaneously restored the pressure to normal. Cushing<sup>17</sup> established the fact that the drinking of water influences the hydration of the cerebrospinal canal. Weed<sup>18</sup> and Kubie<sup>19</sup> demonstrated the close relationship between intravenous hypotonic fluid and cerebrospinal fluid volume. We noted the apparently small volume and low pressure of spinal fluid in many dehydrated surgical patients. Alpers<sup>16</sup> observed that the patients who were susceptible to a postspinal headache developed an unusually low spinal-fluid pressure at the end of withdrawal of 25 c.c. spinal fluid, indicating that they had a low initial volume and a slow rate of re-formation of spinal fluid. All of these points led us to believe that we might decrease the incidence and severity of the headache by increasing body hydration prophylactically. By insuring a positive water balance, especially with water not bound by sodium ions, we might increase the rate of restoration of cerebrospinal fluid volume and pressure so as to offset the loss by dural leakage.

The reported value of posterior pituitary extract in the prevention and treatment of postspinal headache<sup>13, 14, 16</sup> is best explained by its known property of increasing the hydration of the cerebrospinal axis, as shown by its use in the clinical reproduction of epileptiform seizures.<sup>20</sup> There has not been any convincing evidence published to indicate any specific secretory effect of Pituitrin on cerebrospinal fluid. It has been established, however, that posterior pituitary extract is antidiuretic while allowing a disproportionate excretion of sodium ions in the urine. We have therefore employed Pituitrin as an auxiliary means of insuring hydration in the event the patient fails to follow the order to drink ten glasses of fluid a day during the first two days post partum.

The validity of this reasoning has been confirmed by the results obtained by comparing the two series of cases done with the 22 gauge needle. Improved hydration, produced by encouraged drinking of water and three doses of Pituitrin, reduced the probability of a headache from 1 in 4 to 1 in 10. Supportive evidence is afforded by the prophylactic effect of large infusions in preventing headache in every one of the few cases in which such restorative therapy was indicated by clinically evident dehydration or blood loss.

The factor of adequate hydration is very helpful in understanding the following observations:

The relative efficacy of reducing the needle size as compared with increasing hydration is clear. The 24 gauge needle produced a far greater improvement over the 22 gauge control series than did the use of Pituitrin and increased drinking of water.

The use of Pituitrin alone, without the forcing of fluids, was not tested because Zappala<sup>7</sup> and others had found it valueless. In four cases in which Pituitrin was given but water had been inadvertently not encouraged headache occurred in every instance. This experience is not significant; nevertheless, it discourages any idea of a specific value of Pituitrin alone in the formation of cerebrospinal fluid, as was once believed.

Another relevant observation concerning the value of hydration is the finding in five cases that headache was prolonged and severe whenever the obstetrician ordered any dehydration therapy, e.g., oral magnesium sulfate, for relief of a postspinal headache. Such measures, once highly recommended for the treatment of headache due to leakage of spinal fluid, are definitely contraindicated. The aggravation of postspinal headache by dehydration is to be expected in view of the experimental evidence that oral magnesium sulfate lowers spinal fluid pressure<sup>8</sup> and that dehydration increases the frequency and severity of headache experimentally induced by drainage of spinal fluid.<sup>9</sup>

### Discussion

The importance of the size of the dural opening has been stressed in the literature for many years. Yet this essential feature in the best-supported theory of the pathogenesis of common variety of postspinal headache still is not accepted universally. Raney and Raney<sup>10</sup> reject the leakage theory and favor an explanation depending on cervical spinal trauma during positioning for the spinal puncture. Adler<sup>11</sup> stresses the psychogenic causation. Weintraub, Antine and Raphael,<sup>12</sup> who have employed the 22 gauge needle only to continue to meet a high incidence of headache, have lost faith in the leakage theory and have sought some other explanation such as orthostatic hypotension following evacuation of an abdomen distended by a full-term fetus. Compressive abdominal dressings have been tried before<sup>13</sup> with some success but are destined to be of incomplete benefit as long as the fundamental factors of leakage and inadequate re-formation of cerebrospinal fluid are not properly understood. A low cerebrospinal fluid pressure may be temporarily raised by a rise in intra-abdominal pressure. Without reducing leakage or increasing cerebrospinal fluid formation, the prevention of postspinal headache is on an uncertain basis.

The fact which has disturbed many anesthetists who have tried to prevent postspinal headache with the use of a 22 gauge needle is that the complaint has continued to appear in significant incidence despite the use of so fine a needle. The absence of a commercially available 24 gauge needle in this country and the general unawareness of the practicability of a 24 gauge needle have encouraged the belief that the limit of prevention of leakage had been reached. Our experience confirms anew the value and practicability of reducing the size of a dural puncture to that created by a 24 gauge needle.

The fact that headache still appeared in 2.6 per cent of cases punctured with a 24 gauge needle indicates that, if we are to eliminate postspinal headache completely, attention must be directed toward other factors in its pathogenesis. It has long been known that the problem of postspinal headache is complicated by variables other than the size of the dural puncture. The existence of these other determinants of a postspinal headache is suggested by the fact that lumbar puncture even with a 16 gauge needle is not always

that each does not exclude the use of the other. In fact, it is our current practice to use both so as to try for a record even better than the 2.5 per cent noted in the 24 gauge series of cases without increased hydration.

### Summary

1. We have employed the "leakage theory" of the pathogenesis of postspinal headache which may be stated as follows:

- a. Postpuncture leakage permits a fall in cerebrospinal fluid volume and pressure which, in turn, causes dilatation and traction of anchoring, vascular cerebral structures. If this pain-producing process exceeds the pain threshold of the patient, the result is a typical postspinal headache.
- b. Postpuncture leakage is proportionate to the diameter of the spinal puncture needle.
- c. The restoration of cerebrospinal fluid is related to the state of hydration and is decreased by the presence of other demands which compete for body water.
- d. The upright position increases the rate of leakage and aggravates the changes in the cerebral attachments and veins.

2. Postpartum patients, as a group, are more susceptible to the appearance of postspinal headache than any other class of patient for spinal anesthesia because they tend to be more dehydrated, they are more quickly ambulatory, and their pain threshold is lower.

3. The development, rationale, and technique of using a 24 gauge spinal needle are described.

4. The importance of hydration, aided by the antidiuretic factor in Pituitrin, is discussed with relation to its place in the theory of pathogenesis of postspinal headache.

5. The incidence of headache after spinal analgesia for vaginal delivery was studied under controlled conditions to evaluate two important factors, i.e., the diameter of the lumbar puncture needle and the degree of postpartum hydration.

6. A control series of 93 unselected patients who were punctured with a 22 gauge needle and received no increased hydration showed a headache incidence of 26 per cent.

7. Another series of 120 unselected patients who received no increased hydration but were punctured with a 24 gauge needle had a headache incidence of 2.5 per cent, a statistically significant reduction from the control series.

8. A third series of 108 unselected patients who were punctured with a 22 gauge needle but received increased hydration showed a statistically significant reduction of headache incidence to 10 per cent.

### Conclusions

This controlled study of three series of spinal analgesia cases for vaginal delivery demonstrates the exceptional value of using the 24 gauge spinal needle and the principles of hydration to achieve a significant reduction in the incidence and severity of postspinal headache.

1. The incidence of postspinal headache after vaginal delivery is greater (26 per cent) than after cesarean section (8 per cent) despite the use of 22 gauge spinal needles in both types of delivery.<sup>21</sup> This fact has also been reported by Weintraub, Antine, and Raphael.<sup>12</sup> While the presence of wound pain, the postoperative use of morphine and less early ambulation may be part of the explanation, the most likely cause for the decreased incidence of headache after cesarean section is the greater attention to adequate hydration of the cesarean patient, especially with infusion and transfusion.

2. The incidence of postspinal headache after vaginal delivery is greater than after the usual abdominal operations. For example, no headache occurred in our series of 100 consecutive herniorrhaphies performed with spinal anesthesia administered through a 22 gauge needle.<sup>21</sup> Here, too, a valuable prophylactic measure is the more adequate hydration of the surgical patient. The postpartum patient, as a rule, loses more blood and is more dehydrated than one who has undergone an elective hysterectomy or cholecystectomy. Yet the latter type of patient is usually given one or more infusions while the postpartum patient is rarely infused because blood loss of 100 to 250 c.c. during the third stage of labor is normally expected and the further loss of water and blood is so gradual during the flow of the lochia rubra. The majority of patients are more anemic on the fifth day post partum than most postoperative patients.<sup>21</sup>

3. All three of the cases that developed headache in the 24 gauge series suffered blood loss sufficient to lower their hemoglobin determinations on the fifth day post partum to 53, 56, and 58 per cent (Sahli), respectively. The loss in each instance was gradual and therefore no infusion or replacement therapy seemed necessary. Indeed, patients who suffered unusual degrees of dehydration or blood loss seemed especially prone to the development of postspinal headache in the absence of adequate fluid restoration. On the other hand, the patients who received infusions early for any reasons did not have headache, regardless of the size of the needle or the omission of Pituitrin.

The use of increased hydration is especially indicated in preventing or mitigating headache when a lumbar puncture is unavoidably performed with a needle larger in diameter than a 24. The efficacy of hydration, however, is limited. If needles 16 to 20 gauge are used, hydration, unless vigorously enforced, is not likely to be able to restore spinal fluid as quickly as it is lost through the large dural opening. An evidence of this is the finding of 42 per cent headaches in the 16 gauge series of cesarean sections despite routine postoperative infusion with one to two liters of fluid. The finer the needle the less fluid is needed to prevent headache. Even with a 24 gauge needle, however, special attention should be given to improving the hydration of postpartum patients. Too little notice has been taken of the fact that the average obstetrical patient is significantly dehydrated and anemic during the first postpartum week.

Early in this report we discussed the reasons for the high incidence of postspinal headache (26 per cent) when our patients have been punctured with a 22 gauge needle and received routine postpartum care. This incidence is larger than that reported by any other authors. In spite of the fact that the conditions which might influence our results unfavorably have remained the same, our results with the 22 gauge needle and increased hydration or with the 24 gauge needle without hydration are better than the average incidence published by others who have specially studied this subject.

The value of the 24 gauge needle and increased postpartum hydration has been tested by using each measure separately. It is apparent, however,

## OVARIAN NEOPLASMS IN CHILDREN

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OVARIAN neoplasms in children differ from those in adults in several respects: they are more rare in children, they are more frequently incorrectly diagnosed, and they are more commonly associated with complications.

The relative infrequency of ovarian neoplasms in children compared to adults is stressed by Abt<sup>1</sup> who quotes Olshausen as finding only sixty-one ovarian tumors in children under 10 years out of a total of 1,513 ovarian tumors he collected. Witzberger and Agerty<sup>2</sup> found only 186 cases in children under 10 years reported up to 1937. Reviewing 150 granulosa-cell tumors and 66 Brenner tumors in 1935, Bland and Goldstein<sup>3</sup> report eight granulosa-cell tumors and no Brenner tumors in children under the age of 10 years. Lull<sup>4</sup> states that sixteen cases of ovarian tumors showing signs of precocious puberty have been reported up to 1946. Barzilai<sup>5</sup> believes that one-third of 200 cases of dysgerminoma reported have occurred in children and in Novak's series of seventeen cases of dysgerminoma, four were under 15 years of age.<sup>6</sup>

Benjamin<sup>7</sup> states that the first case of ovarian cyst with torsion was reported by Carl Rokitansky in 1842 and one hundred years later Fowlie<sup>8</sup> was able to collect 125 cases of twisted ovarian cysts in children.

The majority of ovarian neoplasms in children, except those producing precocious puberty, are incorrectly diagnosed preoperatively, if a diagnosis is made at all. Since for some unknown reason torsion of ovarian tumors is more common on the right side (twelve of fifteen cases in Sneierson's and Schlesinger's<sup>9</sup> series), the most common mistaken diagnosis is appendicitis; other incorrect diagnoses which have been made are intussusception, mesenteric adenitis, Meckel's diverticulum with obstruction, and pyelitis.

This report includes six cases of ovarian neoplasms operated on in children in a twelve-year period from January, 1936, to December, 1947, at the Queens General Hospital. During this period there were 234 ovarian neoplasms operated upon from a total of 10,413 gynecological admissions. A brief summary of each of the six cases follows.

CASE 1.—M. L., No. 75025, a 7-month-old white child was admitted to the Queens General Hospital on Aug. 20, 1938, because of slight fever and irritability. Her mother stated that following an upper respiratory infection four days ago, the child had continued to cry and draw her legs up on her abdomen frequently. There had been no vomiting and no change in her bowel habits. The past history was not contributory. Examination revealed a temperature of 101.4° F.; there was moderate rigidity on the right side of the abdomen and pressure over this area caused the child to draw her legs up on her abdomen. No mass was felt on rectal examination. The white blood count was 14,800 cells per c.mm. with 84 per cent polymorphonuclear leucocytes. A diagnosis of intussusception was made and the child was operated upon under open drop ether anesthesia.

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to the cyst for at least one year previously. Her symptoms and signs were clear-cut and a correct preoperative diagnosis was made. Pathologic examination of the specimen showed a typical dermoid cyst with hemorrhage following torsion.

CASE 3.—M. A., No. 63157. This 15-year-old white girl was admitted to the Queens General Hospital on Dec. 6, 1939, complaining of pain in the lower abdomen of eighteen hours' duration. She stated that for several years she had cramplike pain in the lower abdomen occurring about every four weeks. Her past history was not remarkable and she had never menstruated. On abdominal examination there was rebound tenderness in both lower quadrants and on recto-abdominal examination a cystic, movable mass was felt on the right side. Her temperature was 99° F. and the white blood count was 7,400 cells per c.mm. with a normal differential count. A diagnosis of ovarian cyst was made and the patient was operated upon on Dec. 11, 1939.



Fig. 1.—Wall of dermoid showing squamous epithelial lining, a sebaceous gland, and some adjacent central nervous system tissue. ( $\times 250$ .)

At operation a mass about 10 cm. in diameter was found arising from the right ovary. The uterus was normal and the left ovary contained several small follicular cysts. A right oophorectomy and an appendectomy were done following which the patient made an uneventful recovery and was discharged on Dec. 24, 1939.

*Pathologic Report.*—The specimen consisted of a cyst measuring 11 by 10 by 5 cm. covered with a smooth, thin wall. On cut section it contained cheesy material and hair; at one area a hard, bony mass was found.

*Microscopic Examination.*—Section showed sebaceous glands embedded in fibrofatty tissue mindful of scalp. A layer of overlying squamous epithelium is present. In another area compact cortical bone tissue can be made out and ossifying hyaline cartilage is seen. Some areas show central nervous system tissue. *Diagnosis:* Dermoid cyst (Fig. 1).

At operation a cyst of the right ovary measuring 6 cm. in diameter was found. A gangrenous area was present on the external surface of the cyst the pedicle of which was twisted and necrotic. The left ovary and the uterus were normal. A right oophorectomy was performed and the abdomen closed in layers without drainage. The child made an uneventful recovery and was discharged from the hospital on Sept. 4, 1938.

*Pathologic Report.*—The specimen consisted of a cystic mass measuring 6.5 cm. in diameter and containing 60 c.c. of dark brown fluid. The wall of the cyst was brown and was thickened at one point where it presents a roughened area. The interior of the cyst wall was smooth except at one area which was thick and covered with a red, friable membrane. Another area presented white calcified tissue.

*Microscopic Examination.*—Section showed some ovarian stromal tissue with massive hemorrhage and an irregular pattern of calcification. The calcified zones varied in size and distribution; some were rounded with psammoma-like bodies, others showed linear calcific areas. An eosinophilic matrix suggested early osseous formation. *Diagnosis:* Cyst with massive hemorrhage and calcification. (This may be an old dermoid although no identifiable tissue can be found in the sections studied.)

*Comment.*—The symptoms in this case were caused by torsion of the cyst pedicle which produced infarction and necrosis of the cyst wall. This child was irritable, had abdominal pain and rigidity, fever and slight leucocytosis. It was not possible to palpate a mass on recto-abdominal examination because of the rigidity of the abdominal wall. Had torsion not occurred in this cyst, it would probably have gone unrecognized for some time. On reviewing the microscopic sections of the cyst only those sections through the calcified area were found, so that no other tissue of a dermoid nature could be demonstrated.

CASE 2.—J. L., No. 97473. This 15-year-old white girl was admitted to the Queens General Hospital on Oct. 5, 1939, complaining of severe pain in the left side of her abdomen of two days' duration. For the past year the pain in her left side had been continuous with frequent exacerbations of a more acute, sharp pain which radiated to her back and down her left thigh. She had no nausea or vomiting, no urinary symptoms, and her bowel habits had been normal. She had begun to menstruate at the age of 13 years, her menses occurring every twenty-eight days and lasting four days. Except for the last two menses which occurred twenty-one days apart, her menstrual history was normal. On examination, her temperature was 99.8° F. and positive findings were limited to abdominal and pelvic examinations. The abdomen was enlarged on the left side and rebound tenderness was elicited in the left lower quadrant. On vaginal examination a large, firm mass was palpated in the left adnexal region. The uterus was anterior and of normal size, shape, and consistency. The right adnexa was not palpable. White blood count was 12,000 cells per c.mm. with 68 per cent polymorphonuclear leucocytes. A diagnosis of twisted ovarian cyst was made and the patient was operated upon several hours after admittance to the hospital.

At operation a large cystic mass arising from the left ovary filled the pelvis; the pedicle was twisted two and one-half times. A left oophorectomy was performed and the abdomen closed in layers without drainage. The patient made an uneventful recovery and was discharged on Sept. 15, 1939.

*Pathologic Report.*—The specimen consisted of a large, blue, cystic mass measuring 15 cm. in diameter. It contained opaque, brown, granular material together with recognizable caseous material, hair, and mucous membrane.

*Microscopic Examination.*—Section showed an area of hyaline cartilage with some marginal gland epithelium and adjacent squamous epithelium. In this region were also present some hypertrophied smooth muscle bundles, fat tissue, and respiratory mucosa. *Diagnosis:* Hemorrhagic dermoid cyst.

*Comment.*—In this girl, too, the symptoms arising from torsion of the cyst pedicle were responsible for her seeking medical aid, although she had apparently had symptoms referable



of the cyst was smooth except for a few papillary projections. The contents of the cyst was a pseudomucinous type of fluid.

*Microscopic Examination.*—Section showed a cyst wall filled with characteristic pseudomucinous epithelium with a sudden transfer to papilliferous and irregular glandular epithelial tissue. In the latter zone the nuclei showed marked variation in size, shape, and orientation to the basement membrane. In another area a more solid, compact papilliferous cellular tissue was found with heaping up of epithelial cells and active mitoses. *Diagnosis:* Pseudomucinous cystadenocarcinoma of the ovary (Figs. 2 and 3).

*Comment.*—This girl's symptoms dated back over two years. The diagnosis of ovarian neoplasm was readily made when she presented herself at the hospital but it was only on microscopic examination of the cyst that its malignant nature was ascertained. Had it been known that this was a malignant tumor at the time of operation, it would perhaps not have been aspirated before removal, and a more radical procedure might have been employed. The question of postoperative radiation arose but the child's family refused further treatment. Thus far, after seven years, no recurrence has taken place.

CASE 6.—B. M., No. A52283. This 13-year-old white girl was admitted to the Queens General Hospital on June 3, 1942, complaining of nausea and vomiting of three days' duration. On May 31, 1942, after swimming she became nauseated and vomited and complained of a pain in the right lower abdomen. Her local physician examined her and, finding a large abdominal mass, sent her into the hospital. Her history revealed that two months previously she had her first menstrual period which lasted two weeks. She never had any vaginal bleeding before or after that episode. Her past history was otherwise not contributory. Examination in the hospital showed a well-developed and well-nourished girl in no apparent pain or distress. The temperature was 99° F., the pulse 80 per minute and the respirations 20 per minute. Secondary sex characteristics were normal for a 13-year-old girl. The positive findings were limited to abdominal and rectal examination which revealed a large, nontender mass filling the entire abdomen. The blood count was normal. Urological examination including x-ray films was normal. A preoperative diagnosis of ovarian cyst was made.

On June 12, 1942, the patient was operated upon and a large ovarian cyst filling the entire abdominal cavity and arising from the right ovary was found. There were about 2,000 c.c. of clear fluid in the peritoneal cavity. The cyst was not adherent but was twisted twice on its pedicle. The left ovary and the uterus were normal. A right salpingo-oophorectomy was performed and the patient made an uneventful recovery, being discharged on June 24, 1942. Follow-up examination to 1947 has shown no recurrence.

*Pathologic Report.*—The specimen consisted of an irregular, oval, soft cystic mass 17 by 16 by 11 cm. Numerous cystic cavities contained clotted blood, others contained a clear watery fluid. All the cavities were lined by a smooth layer of tissue. Between many of the cystic spaces a translucent, soft, yellow tissue was visible.

*Microscopic Examination.*—Section through some areas of tumor showed multilocular cystic foci, some containing blood, and lined by deep-staining, closely placed cells, which resembled granulosa elements in cytology. Some cysts had irregular papilliferous projections which showed a central vessel with radial arrangement of cells mindful of the cumulus oophorus. Some Call-Exner structures were also seen. The cells merged with adjacent stroma in many areas while in some zones the cellular cyst wall lining was sharply delineated. More solid portions of the tumor showed an edematous, fibrillar, and spindle-celled stroma which showed transition to more hypertrophied and hyperchromatic stromal-cell areas. In the latter areas particularly, considerable variation in size and shape of the nuclei was present. Some such areas showed lipoid material in the cytoplasm in abundance. In the cystic areas the nuclei were small and uniform. *Diagnosis:* Granulosa-cell tumor with anaplastic changes (Fig. 4).

*Comment.*—A correct diagnosis of ovarian neoplasm was made in this case. The symptoms of nausea and vomiting were probably due to the twisting of the pedicle which was also associated with sharp lower abdominal pain. Apparently the torsion of the pedicle was not

*Comment.*—This girl's history of lower abdominal pain dated back several years. However, she had never menstruated and the recurrent cramps at monthly intervals may have been due to the engorgement and tension that occur premenstrually. There were no symptoms or signs of torsion and a correct preoperative diagnosis was made on the basis of recto-abdominal examination. The pathologic report showed the cyst to be a dermoid.

CASE 4.—R. O., No. 30519. This 15-year-old white girl was admitted to the Queens General Hospital on March 12, 1941, complaining of pain in the abdomen of twenty hours' duration. For the past six months she had pain in the right lower abdomen at irregular intervals, the pain frequently being associated with nausea but no vomiting. Her menses began at the age of 14 years, occurred every thirty days and lasted four days. Her last menstrual period was two weeks ago. Her past history was irrelevant.

On examination, her temperature was 100° F. The abdomen was not tender and no masses were palpable. Recto-abdominal examination revealed a tender mass in the right lower quadrant. The white blood count was 8,800 cells per c.mm. with a normal differential count. The diagnosis was right ovarian cyst.

On March 17, 1941, the patient was operated upon and a right ovarian cyst measuring 6 cm. in diameter was resected. The appendix was also removed. The patient made an uneventful recovery and was discharged March 21, 1941.

*Pathologic Report.*—The specimen consisted of a rounded cystic mass measuring 6 by 3.5 by 2.5 cm. It was filled with dark red blood clots. The appendix appeared normal.

*Microscopic Examination.*—Section shows a cystic space filled with blood and mucinous material. A fibrous tissue layer with a scant ovarian stroma and a thin adjacent inner corpus luteum layer constituted the wall of the cyst. *Diagnosis:* Simple luteal cyst with hemorrhage.

*Comment.*—Symptoms of right lower quadrant pain brought this girl to the hospital although her history revealed that she had been complaining of irregular lower abdominal pain and nausea for at least six months. The diagnosis in the admitting room was recurrent appendicitis, but after the patient had been observed for several days and a normal temperature and white blood count were noted in addition to the presence of a mass on recto-abdominal examination, a diagnosis of ovarian cyst was made. The pathologic report showed this to be a simple luteal cyst with hemorrhage. Her symptoms were probably of the nature of "Mittelschmerzen" due to rupture of Graafian follicles. Bleeding had occurred into the lumen of the cyst.

CASE 5.—H. F., No. 34002. This 15-year-old white girl was admitted to the Queens General Hospital on May 4, 1941, complaining of abdominal swelling of two years' duration. Two years ago she had noted a slight swelling of the abdomen which had become progressively larger up to the present time. She had slight discomfort but no pain. Her menses began at the age of 12 years, occurred every twenty-eight days and lasted four days. Her past history was not contributory. Examination revealed her temperature to be 98.8° F. The abdomen was enlarged and filled with a cystic mass which extended 5 cm. above the umbilicus. Recto-abdominal examination showed a large mass filling the entire pelvis. The white blood count was 7,200 cells per c.mm. with a normal differential count. X-ray examination of the abdomen was reported as negative.

The patient was operated upon on May 12, 1941, and a large ovarian cyst arising from the right ovary was found. Because of its size it was aspirated before it was removed and 2 L. of a serous fluid were suctioned off. Following this a right salpingo-oophorectomy was performed. The uterus and left adnexa were normal. The patient made an uneventful recovery and was discharged from the hospital on May 24, 1941. Follow-up examination to the present time has shown her to be in excellent health with no recurrence of the tumor.

*Pathologic Report.*—The specimen consisted of a large cystic mass weighing 1,720 grams and measuring 17 by 15 by 10 centimeters. Fibrous septa divided it into numerous small cysts. A small area on the surface showed papillary formation. The inner lining

complete or perhaps it untwisted in the few days before admission to the hospital. The only sign present was the tumor mass in the abdominal cavity. This 13-year-old girl was at the age of puberty so that none of the clinical manifestations attributed to granulosa-cell tumors, such as precocious menstruation, hypertrophy of the breasts, premature appearance of axillary and pubic hair, development of the external genitals and hypertrophy of the uterus were present. It was deemed advisable to be conservative at operation and to follow the patient carefully since the late recurrence of these neoplasms was considered.



Fig. 4.—Area showing granulosa-cell tumor with cystic spaces resembling Graafian follicles. (×360.)

### Discussion

Of the six ovarian neoplasms here reported, two were dermoid cysts, one was probably a dermoid, one was a simple luteal cyst, one was a pseudomucinous cystadenocarcinoma, and one was a granulosa-cell tumor. Torsion of the pedicle occurred in three cases and hemorrhage in three cases. Symptoms had been present for six months or longer in four of the cases and for several days in the two other cases. Pain was the most common symptom and was present in five of the six cases. The most frequent sign was the presence of a mass palpable on recto-abdominal examination, this also occurring in five

Fig. 2.



Fig. 3.

Fig. 2.—Pseudomucinous epithelial lining of cyst wall in a nonmalignant area. ( $\times 250$ .)  
Fig. 3.—Adenocarcinomatous area of cyst wall. ( $\times 440$ .)

2. Four of the neoplasms were benign, two malignant.
3. The most frequent tumor encountered was the dermoid cyst.
4. Complications such as torsion and hemorrhage occurred in four of the six cases.
5. The most common symptom was abdominal pain, which was present in five of the six cases.
6. The most reliable sign was palpation of a mass on recto-abdominal examination.
7. Unless the possibility of ovarian neoplasm is considered in the differential diagnosis of lower abdominal pain in children, the correct diagnosis will be missed.

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of the six cases. Three patients who had an elevated temperature had torsion or hemorrhage in the cyst but the one patient (Case 6) who had incomplete torsion did not have an elevated temperature. There was no alteration in the menstrual cycle in the three patients who were menstruating at the time the tumors were discovered. During the twelve-year period covered by this report, two other 14-year-old girls with functional ovarian cysts were operated upon because of an incorrect diagnosis of appendicitis. One girl had a hemorrhagic corpus luteum cyst measuring 6 cm. in diameter and the other had a cystic ovary containing many follicular cysts which measured 5 cm. in diameter.

In 1937 Witzberger and Agerty<sup>2</sup> collected all ovarian neoplasms reported in children up to 10 years of age. There were 186 cases of which 38 per cent were carcinomas or combined malignancies, 32 per cent were simple or multilocular cysts, 24 per cent were dermoids and 7 per cent were teratomas. Abt<sup>1</sup> states that 60 per cent of ovarian tumors in children are malignant, and Ladd and Gross<sup>10</sup> concur with this figure, adding that of the benign neoplasms 20 per cent are dermoids and 20 per cent are simple cysts.

The case of the youngest patient with a malignant tumor was reported by Ziegler.<sup>11</sup> This was in a 7-month stillborn fetus. The fetus weighed 1,280 grams and was delivered prematurely by breech extraction from a patient with a marginal placenta previa. Both ovaries were entirely replaced by carcinoma. Bulfamonte<sup>12</sup> reported the successful removal of a cystadenoma measuring 15 by 13 cm. from a 36-day-old infant who had presented signs of an abdominal mass since birth. These two cases occurring in infancy are mentioned to emphasize the fact that unless the possibility of an ovarian neoplasm is thought of, the diagnosis will be missed in infants. Since at least 20 per cent of ovarian neoplasms in children are dermoids, x-ray examination of the abdomen may reveal the presence of bone, teeth, calcified material or the translucency of the fatty contents, any of which would be an aid in diagnosis. Hemorrhage from a follicular or corpus luteum cyst should be considered in a girl showing signs of acute appendicitis and the ovary preserved, if at all possible, at operation.

The greatest incidence of granulosa-cell tumors is between 30 and 50 years according to Traut and Marchetti.<sup>15</sup> About 5 to 10 per cent occur before the age of puberty according to Dockerty.<sup>16</sup> One of our six cases had a granulosa-cell tumor but no abnormal clinical manifestations were present.

A freely movable tumor with a long pedicle may undergo torsion, which may occur suddenly or slowly and which may be complete or partial. Torsion results in occlusion of the thinner veins of the pedicle before the more resistant arteries are occluded, so that blood is able to enter the tumor but cannot escape. Perhaps torsion occurs more frequently in children because of their greater activity and because they are more likely to receive trauma to the abdomen or lift excessively heavy weights. Such intra-abdominal causes as vomiting and straining at stool are more common in children too. Taussig<sup>13</sup> states that torsion occurs in 28.6 per cent of the cases in children, a figure much higher than that given by Graves<sup>14</sup> who believes that twisting occurs in 10 to 20 per cent of ovarian tumors of all ages. Frequently, as in two of our cases, it is the torsion that makes known the presence of the tumor.

### Summary and Conclusions

1. Six cases of ovarian neoplasms in children have been reported. These occurred over a twelve-year period during which a total of 246 ovarian neoplasms were operated upon in adults and children.

Results

Each of the two groups contained fifty patients. They were stated to be similar only in that they had placenta previa. Table I shows that their ages were roughly comparable, and that the proportion of primiparas to multiparas was not too different: 20 and 27 per cent. It is of interest that the experimental group had almost twice as many previous babies as the control group. What cannot be shown are the differences in diet, antenatal care, and other advantages which accompany the great differences in social level.

TABLE I. COMPARATIVE STATISTICAL DATA OF THE EXPERIMENTAL AND CONTROL GROUPS

	NUMBER	AGE	PARITY	PRIMIP- ARAS	RACE		METHOD OF DELIVERY
		(YEARS)			WHITE	NEGRO	
Experimental	50	27.5	3.58	20%	40%	60%	Vaginal
Control	50	30.2	1.98	27%	100%	0	Cesarean section

The total number of living babies obtained by the two divergent methods of delivery is roughly the same in both groups: experimental, 62 per cent, and control group, 64 per cent. In Table II, fetuses are separated into weight groups. It is to be noted that in both the experimental and control groups, there are no living babies below 1,500 grams, irrespective of method of delivery. In the group weighing 1,500 to 2,500 grams, the figures are approximately identical; 50 per cent of the fetuses in both groups survived. When the weight of the baby exceeded 2,500 grams, over 80 per cent were living, again with no real difference in the group delivered by cesarean section. This table also brings out the interesting point that 20 per cent of the babies were hopelessly premature, while 50 per cent were at term, consequently were "good risk" babies.

TABLE II. NUMBERS AND PERCENTAGES OF LIVING BABIES WITH REFERENCE TO WEIGHT AND TYPE OF DELIVERY

	TOTAL BABIES		LESS THAN 1,500 GRAMS		1,500 TO 2,500 GRAMS		TERM	
	NUM- BER	PER CENT	NUM- BER	PER CENT	NUM- BER	PER CENT	NUM- BER	PER CENT
<i>Experimental:</i>								
Living	31	62	0	0	6	12	25	50
Dead	19	38	9	18	6	12	4	8
<i>Control:</i>								
Living	32	64	0	0	5	10	27	54
Dead	18	36	8	16	6	12	4	8

Table III shows the type of procedures used in addition to rupture of the membranes. It is noted that in eight cases, not even rupture of the membranes was effected. In most of these individuals labor had progressed so far on admission to the hospital that delivery sufficed to cure the condition. A Willett clamp was applied to the scalp in four instances, and in nine instances version and extraction were resorted to. This latter procedure was utilized only on previable babies and fetuses of borderline viability, and only one living child was obtained.

TABLE III. PROCEDURES USED AS ADJUNCTS TO RUPTURE OF THE MEMBRANES IN THE EXPERIMENTAL GROUP

	NO INTERVENTION	RUPTURE OF MEMBRANES	WILLETT CLAMP	VERSION AND EXTRACTION	CESAREAN SECTION
Experimental	8	42	4	9	0
Control	0	0	0	0	50

with placenta previa, but that these patients in no way differed from those delivered vaginally.

The diagnosis of placenta previa was made in all instances by vaginal examination and, in all, placental tissue was found to be extending over some portion of the external os. No instance of low implantation of the placenta was considered in this series, for although this is merely a less obvious state of the same process, the problems to be solved and the method of handling them would be in no way comparable to those of true placenta previa.

The degree of previa was classified as complete or incomplete. We feel that the method of classification of this condition as marginal, partial, and central is unsatisfactory, for except in the very rare instance of a central placenta previa the amount of placental tissue covering the cervical opening is merely a function of time and cervical dilatation.

The method of delivery varied as to the size of the baby, the amount of bleeding, the degree of completeness of the placenta previa, the configuration of the lower uterine segment, and the presence of other maternal complicating factors. In general, patients whose fetuses were previable or borderline in viability, as determined by the expected date of confinement and the estimated weight of the baby, were allowed to remain in the hospital following a sterile vaginal examination which was done to render a diagnosis of the cause of bleeding but which was carefully and gently carried out to prevent displacement of placental tissue. The decision to deliver these patients and the choice of method were made at the onset of severe bleeding or of labor, whichever process supervened.

Membranes were ruptured whenever possible in the delivery of patients with viable babies or those with previable babies who were definitely in labor or bleeding excessively. If this procedure was not possible *in the previable stage*, the placental edge was perforated and a Hicks version done in a vertex presentation, a foot pulled down in a breech. There was only one complete previa found near term which did not become incomplete with labor; this patient had a cesarean section and is not included in this series.

As for patients with viable fetuses who were in labor but not bleeding excessively, if no clear membrane could be found, they were allowed to continue in labor with close observation. Delivery was effected at complete dilatation, or membranes ruptured at the appearance of clear membrane. At the onset of sudden bleeding, a decision would be made immediately.

Adjuncts to rupture of the membranes such as the Willett clamp and the Beck binder were used in those cases in which the uterine forces were not considered sufficient to apply the fetal head closely to the cervix. Pituitrin in  $\frac{1}{2}$  minim doses was used to stimulate contractions in those cases with inefficient or no labor.

For a control series we were fortunate in obtaining fifty records from a hospital in which cesarean section is done almost routinely on all patients with serious painless bleeding occurring in the last trimester of pregnancy. Records were taken consecutively on all cesarean sections done for placenta previa and performed by qualified and competent obstetricians. Sterile vaginal examinations were done on approximately 30 per cent of these patients, but in no instance was a serious attempt made to rupture the membranes or to carry out any vaginal procedure.

Because of considerable differences in type of patient, social level, and antenatal care, we have avoided detailed analyses of morbidity and incidence of complications other than placenta previa. No prolonged follow-up of either mother or baby was possible, and if both left the hospital alive and well, they were classified as such.



spontaneous delivery is not imminent on admission to the hospital. Another group would reserve the section for those patients in whom simple rupture of the membranes does not suffice. A third school categorically delivers all patients with placenta previa by vagina.

With certain modifications, we belong to the second school of thought. We believe that cesarean section should be reserved for those cases in which the baby is definitely viable, where simple rupture of the membranes does not suffice. Since the fetal mortality rate is so high where the weight is 1,500 grams or less, section should rarely be resorted to, and it should be used with caution in cases where the baby is between 1,500 and 2,500 grams. Naturally it would seem poor economy from the point of view of the fetus to perforate a placenta, perform a version, or pull a foot down when the baby approximates term.

If optimal results are to be obtained by observation of previable fetuses until definite viability is reached, let us stress that certain criteria of care must be fulfilled. The blood supply must be unlimited and immediately available. A "shock team" must be present at all times with equipment and "know how" to run in huge quantities of blood in short intervals. Qualified obstetricians should be in charge and immediately available. The house staff should be able to give a constant and competent supervision at all times. Insurmountable difficulties should be recognized early in attempting vaginal delivery and the line of attack changed. A setup for abdominal delivery should be immediately available.

### Conclusions

A large percentage of patients with placenta previa can be delivered vaginally without undue risk to mother or baby.

Previable babies should rarely necessitate cesarean section for delivery because of placenta previa.

In properly equipped hospitals, borderline viability and previability of the fetus should be an indication for prolonged observation where excessive bleeding or premature labor do not make this impossible.

Further investigation of this problem would be profitable.

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The placenta was perforated five times, and in every instance the perforation was found to be on the margin of the placenta.

There were no maternal deaths. Only one uterus was ruptured, following a version and a mistake in judgment as to the size of the baby. It was followed by an immediate supracervical hysterectomy. This patient was discharged from the hospital on the eighth day without morbidity.

In the cesarean section group there was one death. It was caused by a generalized peritonitis. This infection was incurred in 1942, and only sulfonamides were used as antibacterial agents. It seems likely that this death would not have occurred at the present time.

Discussion

The therapy of placenta previa has been debated since Paul Portal first described the clinical condition and recognized its significance.<sup>13</sup> It may be stated categorically that the inception of cesarean section as a method of therapy for the condition has decimated the maternal mortality and reduced the fetal mortality by 50 per cent. A study of the literary summary included in Table IV, however, shows no direct correlation between the percentage of cesarean sections performed for placenta previa and the fetal and maternal mortality, and it must be noted that hand in hand with this method of therapy have gone blood transfusions and antibacterial agents.

TABLE IV. COMPARATIVE ANALYSIS OF SOME PUBLISHED RESULTS, SHOWING THE LACK OF CONSISTENT IMPROVEMENT IN FETAL MORTALITY WITH VARYING PERCENTAGES OF PATIENTS BEING DELIVERED BY CESAREAN SECTION

AUTHOR	NUMBER OF CASES	GROSS FETAL MORTALITY (PER CENT)	GROSS MATERNAL MORTALITY (PER CENT)	SECTIONS (PER CENT)
Stratz	173	44	0.6	3.4
Brown	3,103	54.2	4.4	8.7
Berkeley	5,107	60	6.2	12.0
Williams	162	31	3	18
Aldridge (Sloane)	215	39.2	4.1	20
Seeley	250	34.6	2.8	23
McAfee	174	23.5	0.57	39
Campbell	325	31	0.6	44
Aldridge (Woman's)	185	40.1	5.9	44.9

Prematurity is the most frequent cause of fetal mortality in placenta previa, as it is of fetal mortality in general.<sup>14, 15</sup> To bring about any considerable reduction in fetal mortality, therefore, we must carry these patients, or as many as is feasible, from the previable and borderline viability stages to approximate term. We are immediately faced with two widely divergent schools of thought: (1) the school which categorically states that all patients with a diagnosis of placenta previa should be delivered immediately regardless of the size of the baby or the general physical conditions extant; and (2) the school which states that patients should be brought, under observation, as close to term as possible unless delivery is forced early by excessive bleeding or the onset of premature labor. Obviously, the fetal premature death rate cannot be reduced by following the first school of thought. It is still too early to tell whether the maternal mortality will be increased by the latter policy, although recent communications tend to belie that impression.

The question of method of delivery is also controversial and tends to be divided into three divergent lines of thought. The first group adheres to delivery of all patients with definite placenta previa by cesarean section when

developed as those seen in the endometrium. In discussing this paper, Brown<sup>2</sup> remarked that, during pregnancy, endometrial implants on the cervical and vaginal mucous membranes could bleed and present an appearance similar to that of carcinoma of the cervix. It is possible that he was referring to the same type of case which we will describe in this paper. If so, we are inclined to disagree with the interpretation that decidua forms in previous endometrial implants because of complete lack of evidence for such a view in our specimens.

We have encountered three cases, two in the cervix and one in the vaginal mucosa adjacent to the cervix, in which the formation of a tumor mass by decidua simulated malignant disease. They appear to represent a clinical entity which should be considered in the differential diagnosis of cervical and vaginal tumors occurring during pregnancy.

### Case Reports

CASE 1.—G. B., aged 33 years, a gravida i, para 0, appeared for examination by her physician in October, 1938, because of increasing vaginal bleeding. Past medical and surgical history was normal. Her previous menstrual history was not unusual, but her last period had occurred the previous June. Examination showed a uterus enlarged to the size of a three months' pregnancy, with a few hard, nodular masses in the anterior wall. There was profuse bleeding from the vagina, apparently from a soft, proliferating mass covering the entire cervix. The impression was that this was definitely a malignancy of the cervix and a biopsy was taken for confirmation.

The pathologist reported, "The sections reveal [Fig. 1] fragments of tissue in which numerous cervical glands are present. The entire stroma shows a very striking transformation into typical decidua of pregnancy. The impression here is that the stroma of the cervix has undergone decidual change in an ectopic site as a result of pregnancy. Diagnosis: Diffuse deciduosis of the cervix."

The pregnancy continued without further abnormality until one month before term, in February, 1939, when a vaginal examination again caused profuse bleeding. A normal spontaneous delivery occurred in March, 1939. A biopsy of the cervix (Fig. 2) was performed in June, 1939, on an area which appeared to be an erosion. The pathological report at that time was as follows:

"The cervix is diffusely permeated by glandular structures which are lined by a single layer of columnar cells of the mucous type, and there is papillary formation in some portions. As a result of this permeation, the cervix is seen to have a spongy structure. The decidual changes observed in the previous biopsy are no longer present. Diagnosis: Diffuse adenomatosis of the cervix."

The cervix was cauterized and healing took place normally. No further abnormality has since developed.

CASE 2.—A 35-year-old gravida ii, para i, three months pregnant, went to her local physician in July, 1946, for obstetrical care and was told, after examination, that she had a "cancer of the womb." Alarmed, she went to a second physician who found a large mass, smooth and apparently covered by vaginal mucosa, filling the posterior fornix of the vagina adjacent to, but not part of, the cervix. He corroborated the clinical diagnosis and referred the patient to a gynecologist, who also thought that the tumor was malignant but performed a biopsy.

The specimen showed (Fig. 3) a definite and marked decidual reaction in a mass of tissue surrounded by fibrous stroma and vaginal epithelium. The patient had an uneventful pregnancy and delivered spontaneously at term. Postpartum examination showed a normal cervix and no residual tumor mass or other lesions in the vagina.

## DECIDUOSIS OF THE CERVIX AND VAGINA SIMULATING CARCINOMA

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**P**ATHOLOGISTS usually think in terms of decidua as contrasted to pseudo-decidua, and of true decidua in normal sites as distinguished from ectopic decidua. At the onset of pregnancy, the stroma of the uterine endometrium shows a striking transformation into decidua, the result of a progressive change beyond the stage of premenstrual hyperplasia, with no sharp demarcation along the way. There have been described, in the absence of pregnancy, pseudo-decidual reactions in the uterus in which the cells closely resemble true decidua. Most interesting, however, is the fact that there can occur, under the stimulus of pregnancy, a transformation of apparently normal cells outside of the endometrium into decidual cells. Changes of this type, developing at a distance from the pregnancy itself, belong in the category of ectopic decidua.

Although it is generally known that decidual cells can appear in the cervix and the vagina during pregnancy, specific instances have not often been recorded. Much less common is the group of cases with which we are here concerned, namely those with decidual masses in the cervix and vagina which may, clinically and pathologically, very closely resemble a malignant tumor, thus leading to serious error by the clinician and confusion for the pathologist who is not aware of the etiology.

In 1906, Taussig<sup>1</sup> reviewed the previous literature and his personal observations on ectopic decidua. He listed 11 possible sites for its occurrence and reported an unusual case of tubal pregnancy with multiple ectopic decidua formation in a parovarian cyst, both tubes and ovaries, the peritoneum, and cervix. There was, however, no tumor formation in the cervix, and he stated that decidua could occur in the cervix distinct and apart from the placental site, contrary to previous belief.

A case of unusual decidual reaction in the cervix was recently described by Hennessy.<sup>2</sup> His patient, a gravida vi, para v, was four months pregnant when a small, bleeding, cervical new growth was discovered. Biopsy showed a marked decidual reaction. She was delivered by caesarean section at 38 weeks, with an uneventful postpartum course.

In a review of five cases of proliferative or papillary lesions of the cervix associated with pregnancy, Edmondson and his associates<sup>3</sup> described none which were decidual in character.

Fluhmman<sup>4</sup> studied eighty-nine cervical lesions in pregnancy, and of this large number none were decidual masses. However, he mentioned the possible formation of decidual islands in the cervix, stating that they were not as fully

The patient was then referred to a gynecologist, who found the uterus enlarged and softened and made a diagnosis of pregnancy. With this information, the pathologist reviewed the slides and corrected the diagnosis to that of decidual reaction in the cervix. Another pathologist confirmed the latter opinion. Without further treatment, the patient delivered spontaneously at term and the cervix was found to be entirely normal on examination six weeks postpartum.



Fig. 3 (Case 2).—Biopsy of vaginal tumor mass. Vaginal mucosa, left upper corner (A). Decidual nodule, right lower corner (B). ( $\times 100$ .)

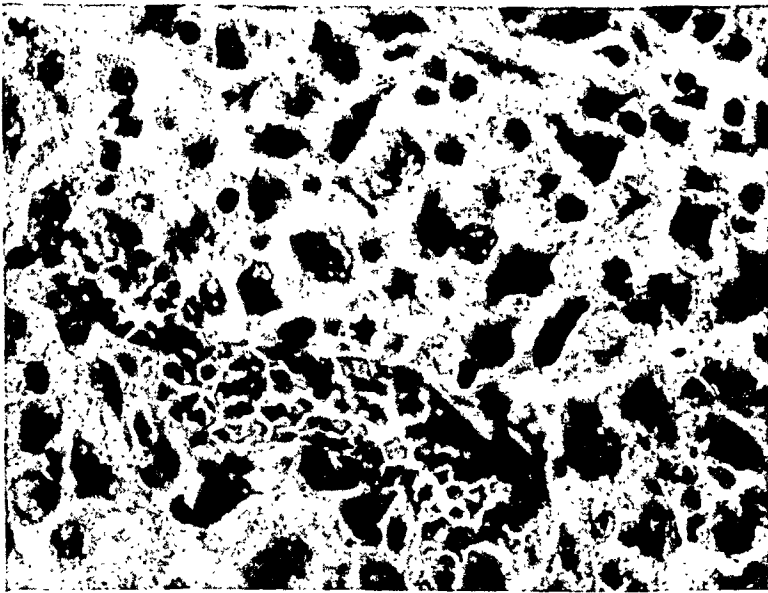


Fig. 4 (Case 3).—Biopsy of cervical tumor mass. The decidual cells resemble anaplastic carcinoma. ( $\times 500$ .)

CASE 3.—A. C., 31 years old, a gravida ii, para i, consulted her family physician in March, 1946, because of two weeks of amenorrhea. Her past medical and surgical history was normal. On routine examination, a large polypoid mass was found covering the external os. The possibility of malignancy was strongly considered and a biopsy was performed. The laboratory report was as follows:

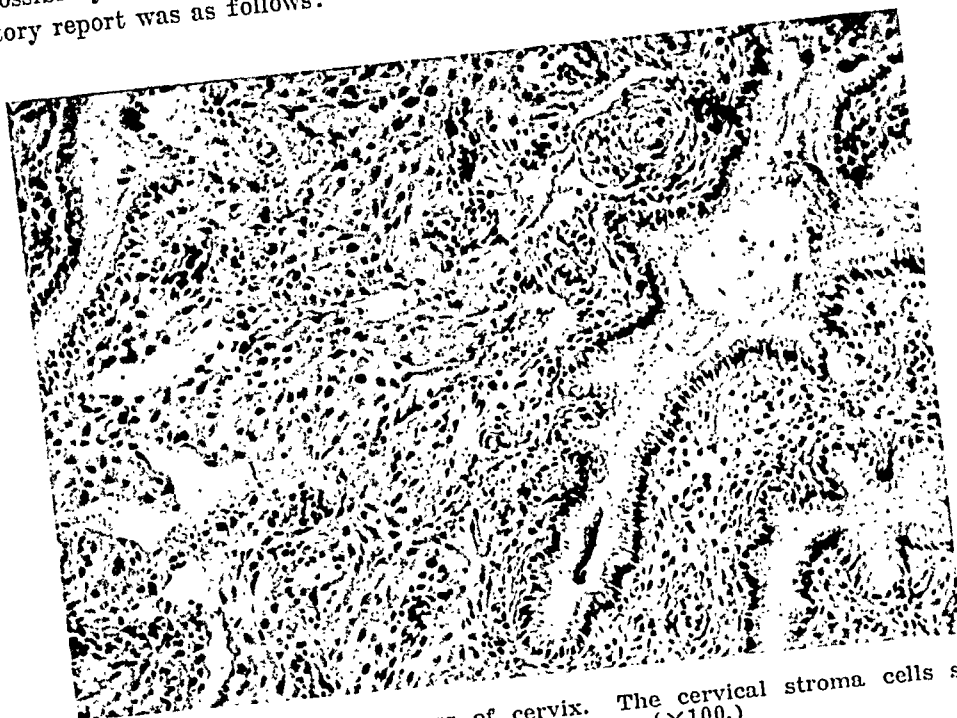


Fig. 1 (Case 1).—Biopsy of tumor mass of cervix. The cervical stroma cells show transformation into true decidua. ( $\times 100$ .)

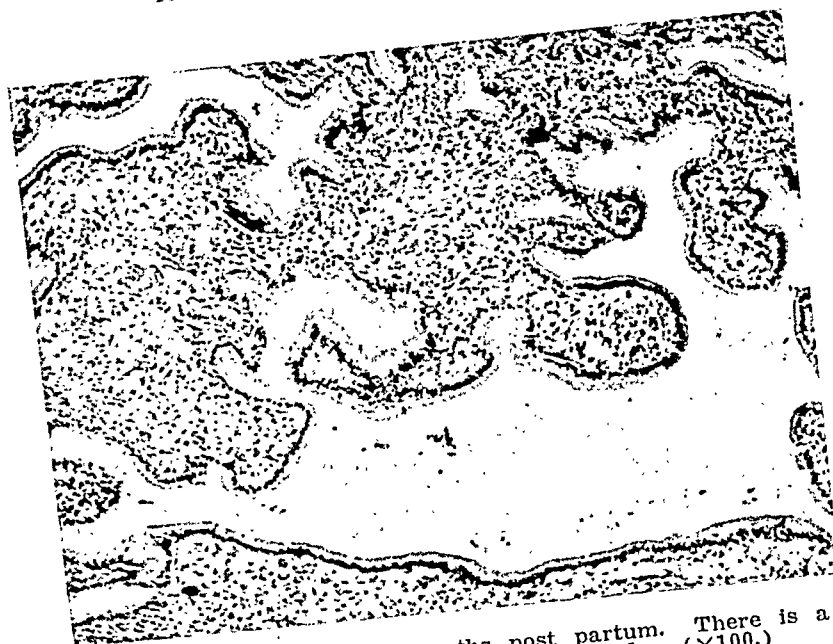


Fig. 2 (Case 1).—Cervical biopsy three months post partum. There is a normal stroma with increased numbers of cervical glands. ( $\times 100$ .)

"The specimen [Fig. 4] consists of several soft, pea-sized masses removed from the cervix. Microscopic examination shows fibrous stroma infiltrated by epithelial hyperplasia with some pearl formation. The cells are hyperchromatic and anaplastic. Diagnosis: Anaplastic carcinoma."

## OCCURRENCE OF UTERINE FUNDUS CARCINOMA AFTER PROLONGED ESTROGEN THERAPY

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IT HAS so far not been definitely proved whether or not the prolonged therapeutic use of estrogenic substances may result in the production of uterine carcinoma in the woman. Fremont-Smith, Meigs, Graham, and Gilbert,<sup>1</sup> in 1946, reported one case, in which adenocarcinoma of the uterine fundus occurred in a woman in the childbearing age. This patient received for the treatment of endometrial hypoplasia between May, 1937, and September, 1945, 392 Gm. of estradiol, 1,085 mg. of estrone sulfate, and 18 mg. of diethylstilbestrol. Uterine curettage in 1942 showed hyperplastic endometrium. Repeated uterine scrapings in 1945 revealed adenocarcinoma of the fundus. In the opinion of Meigs, et al., this carcinoma was directly caused by estrogen therapy.

Notwithstanding, Novak,<sup>2</sup> in 1947, believed that so far no case of human cancer has been recorded in which the evidence for an estrogenic causation is unimpeachable. However, in his opinion it is obvious that estrogen therapy should be held to a minimum or avoided altogether in patients who, because of heredity or through the existence of some other factor (not defined by Novak), may be considered to possess a predisposition to the disease. Novak assumed that the estrogenic factor is not the actual cause of cancer, but rather that the estrogenic stimulation, like any other irritation, is of importance only when superimposed on the still unknown genetic factor.

It is not intended to quote here the literature concerning experimental work on the same subject in animals. It seems to be quite clear, however, that experimental cancer production with estrogens in animals is possible. In view of this, and of the likelihood of an analogous course of events in human beings, it seems pertinent to report observations bearing on the problem. Two such cases will be reported here.

CASE 1.—A 50-year-old white woman was first seen in 1940. She had had irregular periods for the last two years and received medical treatment for hypothyroidism, obesity, and ovarian deficiency. For the last eighteen months she had received injections of Theelin twice a week, often as much as 100,000 units. Three months before, she had a single menstruation-like uterine bleeding, and some spotting since.

Diagnostic curettage on Jan. 13, 1940, resulted in the finding of originally atrophic endometrium with cystic hyperplasia (Fig. 1). The attending physician was verbally informed that the histological changes may be due to estrogen therapy, the discontinuance of which was advised.

However, due to the insistence of the patient, who was quite euphoric while receiving treatment, estrogen was again given in large amounts. During the years from 1937 to 1948, patient received approximately the following amounts of estrogenic substances: 15,000,000 units of Theelin, 600 mg. of Progynon, and 50 mg. of stilbestrol. This is only an estimate, as the patient was known to purchase Theelin without prescription when out of town. On May 20, 1948, she was subjected to another diagnostic curettage because of metrorrhagia. The pathological findings at this time were typical for a malignant adenoma of the fundus (Fig. 2). Subsequent hysterectomy confirmed this diagnosis.

## Discussion

These cases demonstrate that decidual masses or, as we prefer to designate the condition, deciduosis, may occur in the vagina or cervix in such a form that an erroneous clinical or pathological diagnosis of carcinoma can easily be made. For that reason, adequate biopsy and histologic study is essential.

It is apparent that conservative therapy is indicated in all of these cases, and that the outlook is good for normal delivery and complete regression of the tumor within a short period post partum. None of our patients had an associated placenta previa or low implantation of the placenta.

There was no evidence, in any of our cases, to indicate the presence of misplaced endometrial tissue or cells as the site of decidua formation. It is most likely, in our opinion, that the deciduosis arises in ectopic sites as a result of the inherent ability of certain cells to respond to the hormonal stimulus or biochemical changes of pregnancy. The mechanism of this alteration is, of course, unknown.

The differential diagnosis of deciduosis of the cervix and vagina as described here must include, besides carcinoma and other malignant tumors, decidual or placental polyps arising from the endometrial cavity and presenting through the external os of the cervix, as well as benign cervical adenomatous and epithelial polyps. Only by bearing all of the possibilities in mind can an accurate differentiation be made.

## Conclusions

1. Three cases of deciduosis of the cervix and vagina in pregnancy are described in which, clinically, the tumor appeared malignant.
2. Conservative therapy and normal delivery were carried out in all three instances, with complete regression post partum.
3. The condition develops as a form of ectopic decidua, without apparent evidence of pre-existing endometrial implants, and appears to comprise a definite clinical entity.

The author expresses his appreciation to Drs. H. Aranow, H. Gordon, S. B. Gelman, and A. I. Friedman for their aid in furnishing clinical data, and to Drs. J. C. Ehrlich and A. Schwarz for their cooperation in assembling the pathological material.

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Fig. 3.

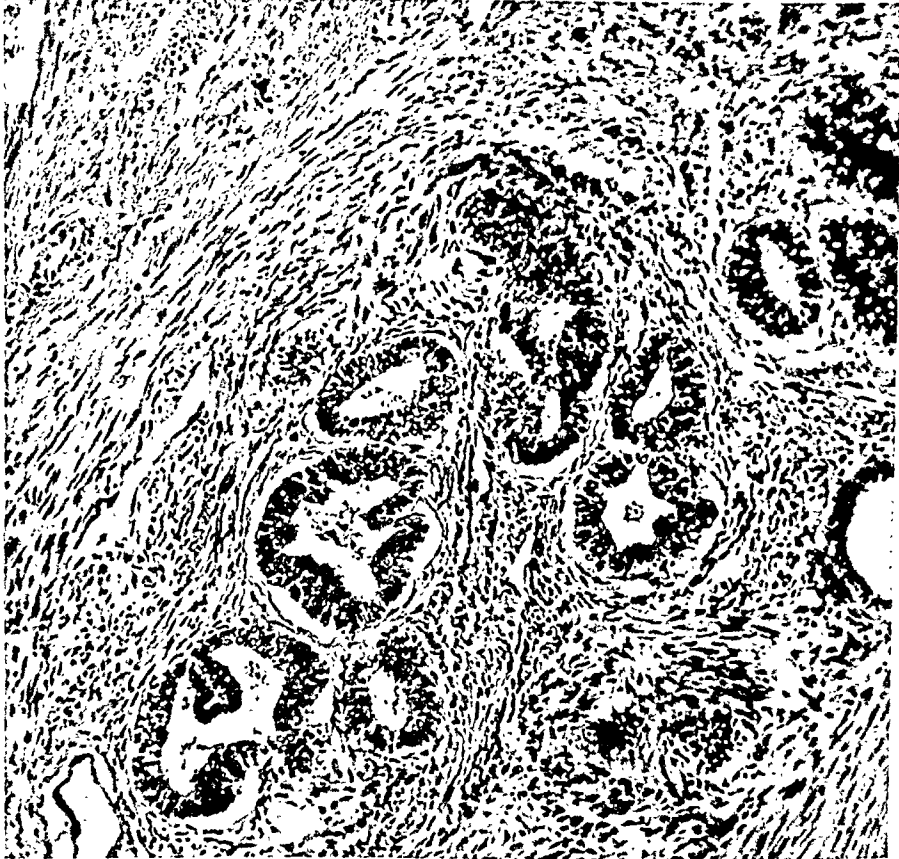
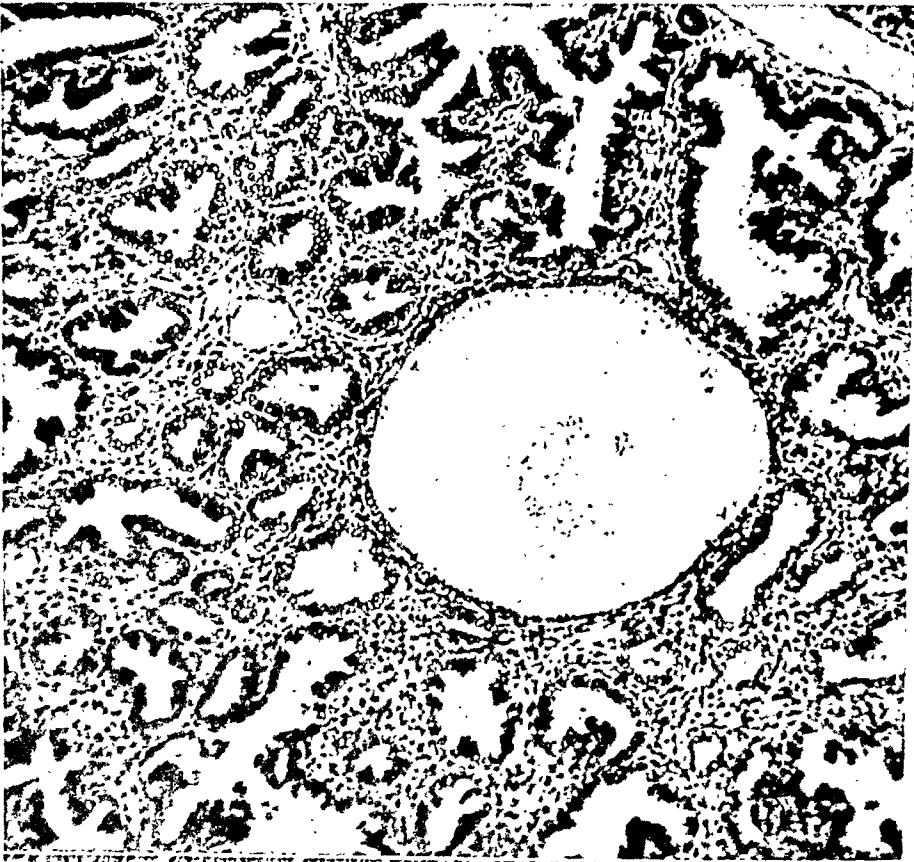


Fig. 4.

Fig. 3.—Superficial portions of adenocarcinoma of uterine fundus seen in curettements. (Appr.  $\times 400$ .)

Fig. 4.—Adenocarcinoma of uterine fundus invading muscularis. (Appr.  $\times 400$ .)

Fig. 1.

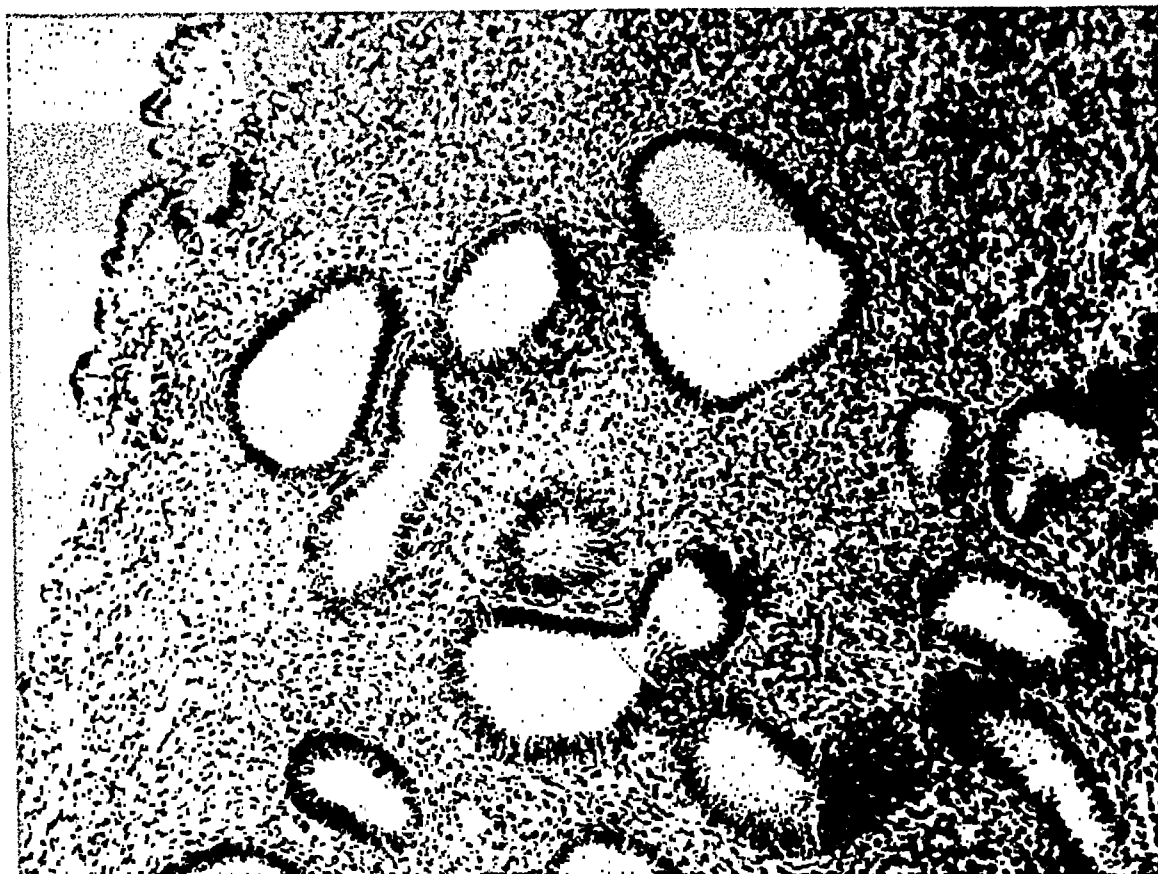


Fig. 2.

Fig. 1.—Cystic atrophy of endometrium with proliferating glandular epithelium. (Appr.  $\times 400$ .)

Fig. 2.—Malignant adenoma of uterine fundus after eleven years of estrogen therapy. (Appr.  $\times 400$ .)

## A BASIC ANALYSIS OF THE OBSTETRIC PELVIS BY ROENTGEN STUDY\*†

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**B**EFORE 1930, our knowledge of the maternal pelvis was based largely on study of the bones by anatomists and anthropologists, and by direct examination of the patient by the obstetrician. In 1932, Caldwell and Moloy<sup>1, 2</sup> devised a classification of the pelvis in which correlation of this older knowledge with roentgen study of the living was attempted. They followed this with a series of studies in collaboration with Swenson and also with D'Esopo.<sup>3, 4</sup> Due credit was given to previous workers such as DeWess (1826), Murphy (1846), Stein (1844), Weber (1830), and Turner (1885). In the early studies the previous workers had recognized more or less the same variations that were later visualized on roentgen study. Caldwell and Moloy gave new impetus to this important problem because by them roentgen study could readily be performed in a large series of cases, and because the findings when taken together with roentgen pelvimetry and the other obstetrical data are of real practical value.

They divided the pelvis into anthropoid, gynecoid, platypelloid, android, and asymmetric types. They also recognized that there occurs an overlapping of these types. I shall not attempt to describe these in detail. Instead, I shall present my own findings in the analysis of over 10,000 roentgen studies of pregnancy and bring out fundamental principles and a simplified approach.

In rendering a written description of the pelvis I have found that I could not adequately describe the various parts by following the terminology of Caldwell and Moloy. The types overlap to a marked degree and the extent of type varies. If the pelvic inlet were described as moderately android in the posterior segment and gynecoid in the anterior segment, I found that few would have a clear picture. However, when I began to classify the various parts of the pelvis in simple geometric terms, giving the degree, the reports were readily understood. The practical significance of these shapes may be easily recognized although the etiology is not clearly understood.

*Inlet.*—In trying to describe the pelvic inlet in geometric terms I found that the outline of the posterior segment is either trilateral or rounded in varying degree, and that the outline of the anterior segment is either rounded or wedged in varying degree. Roentgen study of the pelvis in 50 males shows that for the posterior segment, trilateral shape has an incidence of 86 per cent and for the anterior segment, wedged shaped is 84 per cent (Table I). Analysis of 1,000 consecutive female roentgen pelvimetries shows rounded anterior and posterior segments in 80 per cent and wedged anterior plus trilateral posterior segment in 20 per cent. Therefore, it is safe to assume that the trilateral shape and wedging are male characteristics and that rounding is a female characteristic (Table II).

\*Most of the material was obtained from Harlem Hospital Obstetric Service, Bronx Hospital Obstetric Service, and from the Radiology Departments of the Bronx and Harlem Hospitals.

†Presented June 9, 1948, at the Annual Meeting of the American Medical Association, Chicago, Ill.

CASE 2.—A 35-year-old white woman was first seen on Feb. 27, 1947. She had been married for twelve years and was never pregnant, although she desired children. Her menstrual periods had always been irregular. For the last two years she had had menorrhagia. Several physicians, who saw her during this time, thought the condition to be menopausal. One physician, however, had told the patient two years before that she had an ovarian cyst. Nevertheless, she was given estrogen therapy. The amount and kind of hormones pre-operatively used are not known. For the past two to three months the menorrhagia had increased and had been accompanied by pain in the left lower abdomen. Physical examination revealed a slightly enlarged uterus; a movable tumor mass was felt in the left adnexal region. A laparotomy on Feb. 28, 1947, revealed bilateral enlargement of the ovaries, which were removed. They measured 6 by 5 by 4 and  $5\frac{1}{2}$  by 4 by  $2\frac{1}{2}$  cm. On sections the usual number of follicular and corpus luteum cysts was present. However, the stroma was of a yellowish color and abundant. Microscopic examination revealed that the solid areas of both ovaries were occupied by theca cells. The pathologic diagnosis of theca-cell tumors of both ovaries was made. No uterine curettage was performed at this time. Subsequent to the bilateral oophorectomy estrogen therapy was instituted: 120,000 units of Theelin and 140 mg. of progesterone were given from March 2, 1947, to Oct. 17, 1947, at which date the patient was subjected to a diagnostic curettage because of recurring metrorrhagia. Microscopic examination of the uterine scrapings revealed a malignant adenoma of the fundus (Fig. 3). Total hysterectomy was performed on Jan. 13, 1948, and the diagnosis was confirmed. Invasive tendencies of the tumor into the muscularis were noted (Fig. 4).

### Discussion

In the first case a woman beyond the menopause received large amounts of estrogenic substances for approximately ten years. Histological and clinical evidence exists that after two years of this therapy the glandular epithelium of the uterine fundus showed proliferative tendencies. After ten years of therapy the proliferative tendency became uncontrolled. This sequence of events can be at best compared only with an uncontrolled experiment, but is nevertheless highly suggestive in view of the well-known effects of estrogenic substances on the uterine mucosa.

In the second case there is less suggestive evidence, as it is well known that theca-cell tumors or theca-cell hyperplasia of the ovaries often result in endometrial hyperplasia or malignant adenoma of the fundus. However, also in this case, the sequence of events is quite important, in view of the appearance of the fundus carcinoma several months after bilateral oophorectomy and "substitute" estrogen therapy.

In view of the moral and technical difficulties preventing us from obtaining more definite evidence of the role of estrogens in uterine carcinogenesis in human beings, such cases as these should nevertheless be regarded as a warning against the therapeutic use of estrogens in a promiscuous manner, at least until definite proof exists that they are not carcinogenic.

### Summary and Conclusion

Two cases of uterine fundus carcinoma occurring after prolonged administration of estrogens are reported. In both cases the sequence of events, together with the known properties of estrogens, strongly suggests an etiological relationship. For this reason it is believed that there should be no promiscuous therapeutic use of estrogens.

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which means that the anteroposterior diameter of the inlet tends to become shortened. Poor metabolism of estrogen<sup>7, 8, 9</sup> with high blood level due to vitamin B and liver deficiency might be a factor. Excessive estrogen causes bone demineralization in rats. In human beings, excess estrogen as in famine conditions causes osteomalacia with bone softening resembling parathyroid overactivity. This is not to be confused with the generalized osteoporosis following menopause where loss of estrogen eventually causes overactivity of the adrenals leading to a negative nitrogen balance. Severe starvation causes osteomalacia during puberty and pregnancy. Lack of protein in the diet may contribute to poor bone nutrition, since a negative nitrogen balance eventually evidences bone demineralization. The changes of the sacrum and pelvis may, therefore, be considered to be due to a mild form of osteomalacia. In male pelvimetry studies that I have done, the Turner Index tends to be higher than in females, indicating better bone nutrition on a hormonal basis. Testosterone favors strengthening of bone, probably by favoring a positive nitrogen balance.

The sacrum may be short or long depending on the number of spinal segments that are sacralized. Since this is developmental, determined during fetal life, and, since Warkany<sup>10</sup> has produced bone malformations in rats by causing vitamin B deficiency, it is possible that a causal relation exists and that future generations may not present this sacral variation (Fig. 1).

These suggested etiologies of variations of the pelvic architecture, (1) hormonal, (2) developmental, and (3) nutritional, are appealing because they offer a basis for possible control in future generations.

*Ischial Spines.*—In males the spines are large in 70 per cent, medium in 22 per cent, and small in 8 per cent. It is safe to assume that large spines in the female pelvis are indicative of malelike quality.

*Lateral Wall Convergence.*—In males the lateral walls are funnel in 68 per cent, moderately convergent in 24 per cent, and slightly convergent in 8 per cent. In females funnel shape occurs in only 10 per cent, moderate convergence in 40 per cent, and slight in 50 per cent (Fig. 1).

*Subpubic Notch.*—The subpubic notch in males is small in 96 per cent of cases and in females in 25 per cent. In males it is medium in 4 per cent and in females in 35 per cent. In males I have found no large subpubic notches and in females the incidence is 40 per cent (Fig. 1).

TABLE III. TYPICAL ANDROID PELVIS. INCIDENCE 114 OUT OF 1,000 (12 PER CENT)

Inlet	Anterior segment, wedged
A. P. View	Posterior segment, trilateral
Sacrum	Shallow or rounded
Lateral View	
Spines	Large
A. P. View	
Lateral walls	Funnel
A. P. View	
Subpubic notch	Small
A. P. View	
Sacrosciatic notch	Small
Lateral View	
Acetabular bulge	Seen occasionally
A. P. View	

As stated previously, for the sake of greater accuracy, out of the total 10,000 cases, I made a statistical review of 1,000 consecutive roentgen studies of the female pelvis, made during late pregnancy. I was able to find what I considered to be a pure female pelvis in 30 per cent of cases, as outlined in Table II. Likewise I was able to find a pure android pelvis in 12 per cent of cases

TABLE I. MALE PELVIS. (50 CASES)

Inlet.—		Posterior Segment.—		Anterior Segment.—	
A. P. View.		Trilateral,	86 per cent	Wedge, 84 per cent	
		Rounded,	14 per cent	Rounded,	16 per cent
Spines.—	Large,	70 per cent	Medium,	22 per cent	Small, 8 per cent
A. P. View					
Lateral Walls.—	Funnel,	68 per cent	Moderate 24 per cent	Slight con-	8 per cent
A. P. View			conver-	vergence,	
			gence,		
Subpubic Notch.—	Very	36 per cent	Small,	60 per cent	Medium, 4 per cent
A. P. View	small,				
Sacrum.—	Curved,	24 per cent	Shallow,	60 per cent	Convex, 16 per cent
Lateral View			Ridged,	10 per cent	

TABLE II. TYPICAL GYNECOID PELVIS. INCIDENCE OF 306 OUT OF 1,000 CASES  
(30 PER CENT)

Inlet	Posterior segment, rounded
A. P. View	Anterior segment, rounded
Sacrum	Curved
Lateral View	
Spines	Small
A. P. View	
Lateral walls	Moderate convergence
A. P. View	
Subpubic notch	Large
A. P. View	
Sacrosciatic notch	Large
Lateral View	
Acetabular bulge	None
A. P. View	

In order to retain common terminology the fully female type inlet may be designated as gynecoid and the male type as android. The deeply rounded anterior and posterior segments of the inlet with deep anteroposterior diameter and narrow transverse diameter were designated as anthropoid by Caldwell and Moloy. According to the classification given here this may be safely grouped with the gynecoid, providing pelvic measurements are added.

The platypelloid pelvis of Caldwell and Moloy is characterized by rounded anterior and posterior segments of the inlet with a very low Turner Index, that is, a shallow pelvis with a relatively small true conjugate. I prefer to class this also as gynecoid and depend upon the pelvic measurements for further clarification. The shallow inlet in my experience appears to be due to poor bone nutrition as described elsewhere in this paper (Fig. 1).

**Sacrum.**—In the female, on the lateral roentgen view, the sacrum is curved in 45 per cent of cases, shallow in 30 per cent, and flat to convex in 25 per cent. In males the incidence is: curved, 24 per cent, shallow, 60 per cent, and convex, 16 per cent.

It would appear that shallowness indicates a tendency toward the male quality. However, shallowness may be akin to flatness or convexity, which are apparently due to deficient bone nutrition. In marked cases the upper portion of the sacrum is flat to convex and the promontory dips forward. The lower portion of the sacrum dips backward and may be sharply curved forward.

There are probably other causes, besides rickets, of disturbed bone nutrition which affect the sacrum. In 1939, Greulich, Thoms, and Twaddle<sup>5, 6</sup> showed that white female children have a high Turner Index (true conjugate divided by transverse of inlet). Later in life this index becomes reduced in some women,

as outlined in Table III. It is important to recognize that 58 per cent of cases showed a mixture or overlapping of the two types in varying degree as shown in Table IV. It has, therefore, proved simplest to describe each factor of the pelvis independently using geometric terms as shown in Table V. Asymmetry of the pelvis is rare and is usually caused by old fracture, bone infection of the hips, extreme scoliosis, or poliomyelitis.

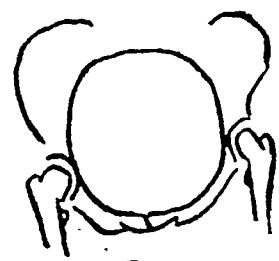
TABLE IV. MIXED PELVES (ANDROID AND GYNCOID). INCIDENCE 580 OUT OF 1,000 CASES (58 PER CENT)

Inlet A. P. View	Pure, 43 per cent. (Anterior and posterior segment rounded or anterior segment wedged with posterior segment trilateral.)  Mixed, 57 per cent. (Anterior segment rounded with posterior trilateral or anterior segment wedged with posterior rounded.)
Spines A. P. View	Small, 56 per cent, Medium, 20 per cent, Large, 24 per cent.
Lateral walls Convergence A. P. View	Slight, 62 per cent, Moderate, 22 per cent, Marked, 16 per cent.
Subpubic Notch A. P. View	Wide, 22 per cent, Medium, 22 per cent, Small, 56 per cent.

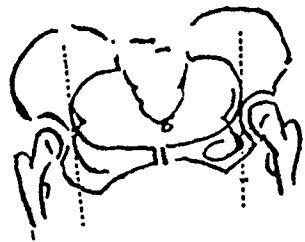
TABLE V. PELVIC ARCHITECTURE

Inlet A. P. View	Anterior segment rounded (gynecoid) slight, moderate, deep wedged (android) slight, moderate, marked  Posterior segment round (gynecoid) slight, moderate, marked trilateral (android) slight, moderate, marked
Sacrum Lateral View	Curved (gynecoid) Shallow (android) Flat to convex upper portion Lower part of sacrum forced back and coccyx angulated forward (poor bone nutrition) Ridged (android)
Ischial spines A. P. View	Small (gynecoid) Large (android)
Convergence lateral walls A. P. View	Straight, slight, moderate (gynecoid) Funnel (android)
Subpubic notch A. P. View	Large (gynecoid) Small (android)
Bulge acetabulum A. P. View	None (gynecoid) Present in males about 10 per cent
Pubic lips A. P. View	Small and light (gynecoid) Large and heavy (android)
Sacrosciatic notch Lateral View	Wide (gynecoid) Narrow (android) Wide in lower part associated with back sweep of sacrum (poor bone nutrition)

In order to bring out the relative value of roentgen analysis of the pelvic architecture a brief outline of some of the causes of dystocia follows:



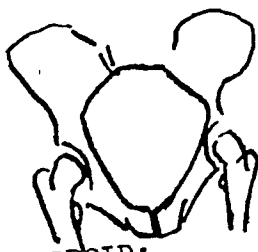
GYNECOID:  
Inlet  
Post. seg.--round  
Ant. seg.--round



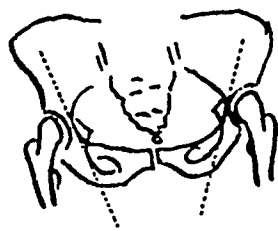
GYNECOID:  
Lat. walls--slight or moderate, convergence  
Spines--small  
Subpubic notch--large



GYNECOID:  
Sacrum---curved  
Sacro-sciatic notch--large



ANDROID:  
Inlet  
Post. seg--trilateral  
Ant. seg--wedged



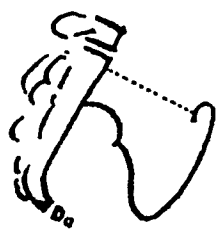
ANDROID:  
Lat. walls--funnel  
Spines---large  
Subpubic-notch-small



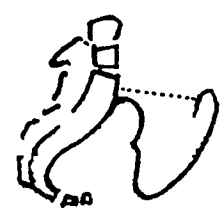
ANDROID:  
Sacrum---shallow  
Sacro-sciatic notch--narrow



POOR BONE NUTRITION  
AS RICKETS: Moderate



AS RICKETS: Marked



AS RICKETS: Severe



SACRUM: Short



SACRUM: Double promontory



SACRUM: Long

Fig. 1.



## THE PATTERN OF UTERINE GROWTH DURING PREGNANCY IN MONKEYS AS SHOWN IN AN X-RAY STUDY\*

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CONSIDERABLE interest has been evidenced in recent years by gynecic physiologists and by clinicians in growth patterns of the gravid uterus.<sup>1-10</sup> Observations by one of us,<sup>3-6</sup> chiefly upon the rabbit, led to a new impression concerning uterine accommodation of the products of conception. Briefly stated, these observations support the belief that there are, in litter-bearing animals, three distinct periods of uterine growth during gestation. These are, namely:

a. *Preparation*.—This consists of proliferation of endometrium and myometrium under the influence of progesterone and it diminishes about the time of nidation.

b. *Hypertrophy and Hyperplasia*.—Increasing intrauterine tension due to the enlarging fetus constitutes a growth stimulus by which all uterine elements grow.<sup>11</sup> The general shape of the conceptus sites in this stage is spherical. Tension within the uterus mounts rapidly due to hydrostatic forces cited elsewhere and beyond a certain point this tension has a deleterious effect causing reduced blood-flow through the uterus<sup>5</sup> and ischemia of the myometrium.<sup>3</sup> The degree of circulatory impairment to the uterus increases as growth in the spherical form continues and a critical point is reached.

c. *Elongation*.—The critical phase described above is relieved abruptly by a physiological mechanism which has been termed conversion. The essence of conversion is that the conceptus sites rapidly elongate into a cylindrical shape, thereby reducing the intrauterine tension. This is attributable to forces operating in accordance with established hydrostatic principles.<sup>4</sup> Blood-flow through the myometrium thereafter is again rapid. Since tension served as the stimulus for uterine growth, it is obvious that the diminution of tension associated with the change of shape removes to a large degree this stimulus. Therefore, enlargement of the cylindrical uterus is accomplished by stretching of myometrial elements already present with minimal growth of new tissue. Consequently, this period comes to a self-limiting end under normal conditions, when stretch limits are approached. The fetus grows rapidly in the tubular uterus and it seems possible that the maturity of a given species at birth is directly proportional to the relative amount of its gestational period that is spent in a converted uterus.

These findings are rather well documented in litter-bearing animals<sup>12</sup> and will not be further elaborated upon here. The purpose of this paper is to ana-

\*Read by invitation, before the Baltimore Obstetrical and Gynecological Society, Feb. 11, 1949.

†Carnegie Fellow.

### CAUSES OF DIFFICULT ENGAGEMENT

#### 1. Poor shape of inlet:

- (a) posterior segment trilateral (android)
- (b) anterior segment wedged (android)
- (c) posterior segment of inlet flattened (poor bone nutrition, usually seen with flat to convex sacrum)
- (d) asymmetry (rare)

#### 2. Small measurements of inlet (common)

#### 3. High, double, or forward promontory (poor bone nutrition and/or developmental, occasional)

#### 4. Soft part interference: pendulous uterus, full bladder or rectum, polyhydramnios, fibroids, ovarian cyst, placenta previa, abdominal pregnancy, short cord, or cord twisted about fetus

#### 5. Fetal head, too large, too firm, malformed

#### 6. Malpresentation (usually associated with above factors)

### DIFFICULTIES AT THE MIDPELVIS

#### 1. Sacrum, shallow, ridged (android)

flat or convex (nutritional)

#### 2. Ischial spines, large (associated with small interspinous measurements, android)

#### 3. Funnel lateral walls (android)

#### 4. Poor flexibility of tissues (elderly primipara, defective nutrition)

#### 5. Small pelvic measurements (common)

#### 6. Fetal head, too large, too firm, malformed

### Summary

In review, it would seem that the important basic influences on the pelvis are:

1. Hormonal, resulting in gynecoid (female), android (male), and mixed types.

2. Developmental, which influence on the pelvis is recognized largely at the present in the degree of sacralization of the sacrum.

3. Nutritional, commonly rickets. Also, vitamin B deficiency may cause excess accumulation of estrogen by deficient liver function, leading to calcium mobilization and weakening of bones.

4. Injury or infection, as with osteomyelitis. This may cause asymmetry of the pelvis, an uncommon finding.

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Fig. 2.—Lateral soft tissue x-rays of uteri at progressive intervals through gestational period. The general appearance before the 100th day is spherical and thereafter becomes cylindrical. The radiopaque markers are visible in some plates. It has been necessary to ink in outlines because of loss of contrast in photography and reduction. Upper left, 59 days, upper right, 78 days, lower left, 99 days, lower right 104 days.

lyze data concerning the growth patterns in the primate uterus in order to ascertain to what extent conditions similar to those prevailing in the uterus duplex of the rabbit pertain to the uterus simplex.

### Methods and Materials

The investigation was in two separate phases consisting of: a. an analysis of soft tissue x-ray outlines of pregnant monkey uteri, and b. weighing fixed specimens of fetuses and uteri at various gestational ages.

a. In the x-ray study six pregnant rhesus monkeys (*Macaca mulatta*) were used. Of these, two aborted and one was sacrificed on the ninetieth gestational day for other purposes of the study. Each animal was subjected to laparotomy early in pregnancy (between the thirty-sixth and sixty-eighth days) at which time radiopaque substances (silver sequins and silver wire) were sewn at predetermined points to the gravid uterus. At the same time a metal clip was fastened to the posterior lip of the cervix. It was following these procedures that two of the animals aborted. The remaining four were subjected to soft tissue x-rays of the abdomen, both anteroposterior and lateral views being obtained. X-rays were taken at frequent intervals throughout the remainder of these pregnancies. It was soon found that for purposes of outlining the uterus, the anteroposterior views were of limited assistance. Further, the radiopaque markers shifted greatly in position as growth continued and they could not be used as guides in reading x-rays. Consequently, the results are based on lateral views of the uterus without the use of markers.

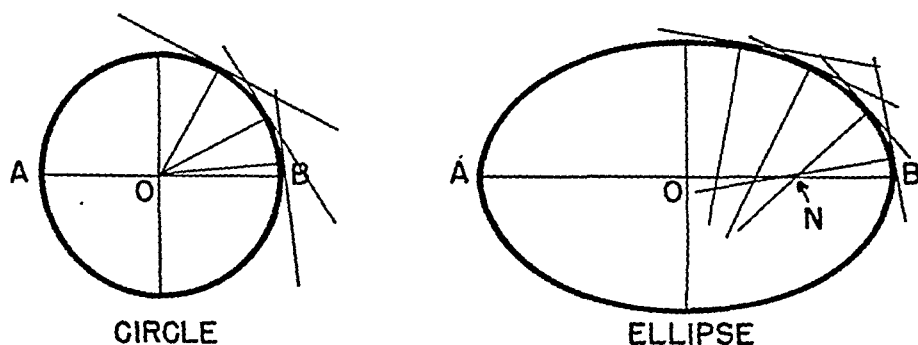


Fig. 1.—Method used in obtaining projection ratio (ON/OB) in the analysis of various curves. The line AB representing greatest length is bisected at O, the perpendicular extended from O (OD) dividing the figure into four quadrants. Tangents are drawn to curves of the two upper quadrants and perpendiculars from these are extended till they cut OB. The outermost tangent cut is called N and the ratio ON/OB approaches 1 as the organ increases in cylindrical shape. In the circle,  $ON:OB = 0:25$  or 0, whereas, in the ellipse shown,  $ON:OB = 22:42$ .

In each series the x-rays were placed on a horizontal viewing box and the outline of the uterus was accurately transferred to paper by means of a suspended precision pantograph. The curves of the lower quadrants were difficult to visualize in many instances but were not important in the calculations. The drawings were analyzed as indicated in Fig. 1 which shows the principle applied to a circle and an ellipse, respectively. A line was drawn joining the highest point of the fundus to the cervix. AB was bisected and a perpendicular erected (CD) which divided the uterus into four quadrants, of which the posterior and anterior upper ones were used. Tangents were drawn to the curvatures of these quadrants and perpendiculars erected to the tangents. The perpendiculars were extended till they cut the line AOB and the outermost perpendicular cuts AOB at N. It is obvious that if the uterus were a perfect

sphere, all perpendiculars would pass through O. The value ON would be zero, and the ratio ON:OB would be zero. As the uterus becomes cylindrical, the line ON lengthens and the value ON:OB approaches 1:1 or 1. This method eliminates changes in size of the uterus as a factor in the determination. The values ON:OB were plotted on semilogarithm graphs as actual ratios.

b. Specimens consisting of fixed monkey fetuses at various gestational ages and their uteri, empty of contents, were carefully weighed and allowance made for fixation.

## Results

### *X-ray Studies.—*

a. Superficial scanning of the x-ray plates (Fig. 2) suggests strongly that a change in uterine shape has occurred between the 100th and 105th days of gestation. This observation is more obvious when a series of pantograph transfers are examined. Finally, in removing the observations from the realm of visual judgment to that of logarithm graphs, the results are equally clear (Fig. 3). The graphs indicate that on or shortly after the 100th day there is a fairly rapid elongation of the uterus as it tends to approach a cylindrical shape which it retains for the remainder of gestation. The exact length of time it takes to complete this process cannot be determined from these observations except to say it is less than five days. Conversion occurs rapidly in the rabbit, i.e., in about two hours but is probably somewhat longer in primate uteri.

b. In Fig. 4 is plotted the gain in weight of fetus and uterus throughout gestation of the monkey. The figures were obtained as mentioned previously by weighing material from the Carnegie collection and they follow the pattern of other observers inasmuch as is possible to demonstrate.<sup>14</sup> It will be noted that the curve representing uterine weight flattens out following the 100th day. This is to be expected if growth has diminished and actual stretching instituted as suggested by the x-ray study above. Further, it can be seen that the fetus about the same time begins to increase in absolute weight rapidly, regardless of the percentile increment gain which is, naturally, always decreasing.<sup>15</sup> This marked increase in absolute weight following conversion has been shown to hold true in other species and is believed due to an interaction of several factors, not the least of which is the reduction of intrauterine tension and improved circulation.

## Discussion

From the data presented it seems possible that at a uniform time and in a relatively short period of time the gravid monkey uterus changes from a predominantly spheroid to a predominantly cylindrical organ. What further evidence is there that this actually takes place?

Studies have been carried out in monkeys which show that before the 100th day of gestation, the endo-myometrial arteries proliferate greatly and become closely coiled. This is demonstrated diagrammatically in Fig. 5. The coiling appears to be in excess of current demands of the organ. Following conversion (at or shortly after the 100th day) an abrupt transition of this vascular pattern supervenes. This consists of rapid uncoiling along the whole length of the arteries so that they become completely straight except for an occasional right angle turn. Obviously some event has taken place which has made these vessels pay out and it is apparent that the coiling had been in preparation for this event. These observations, made prior to the investigations into changing

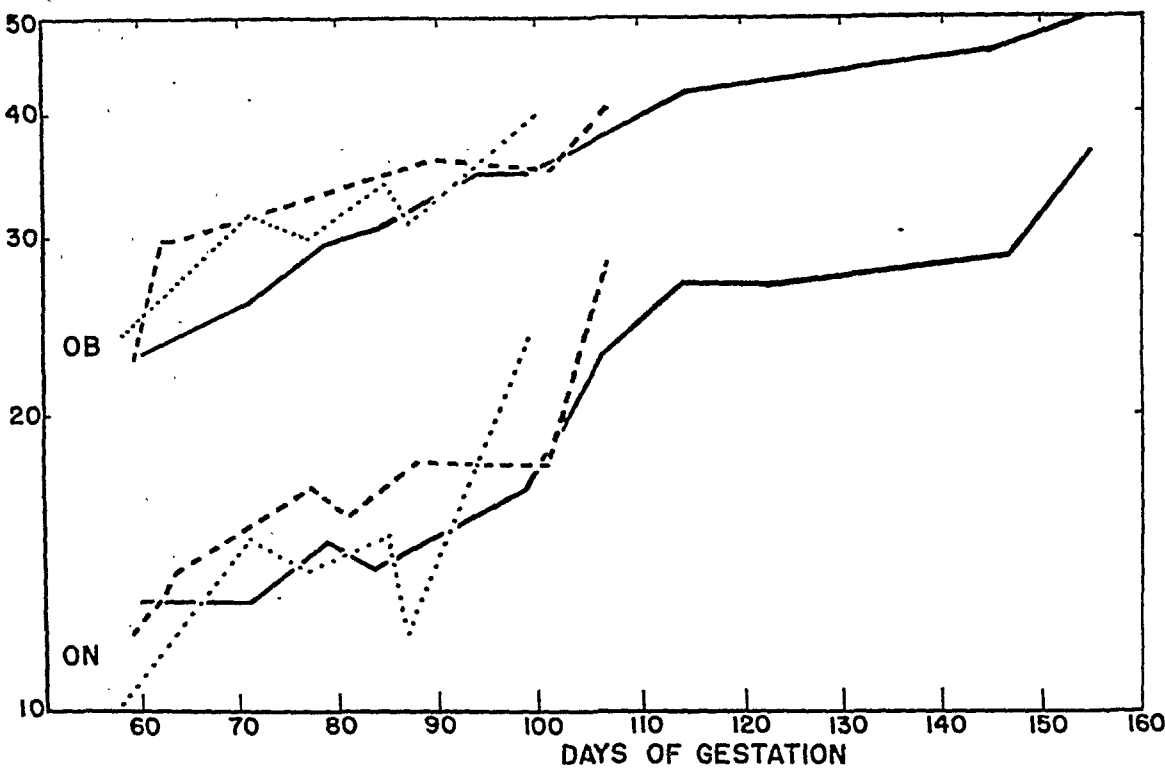


Fig. 3.—Logarithm graph representing curvature of anterior upper quadrant. As the lower line (ON) approaches the upper (OB) the uterus is becoming cylindrical. Note that in all specimens there is a sharp upward curve around the 100th day.

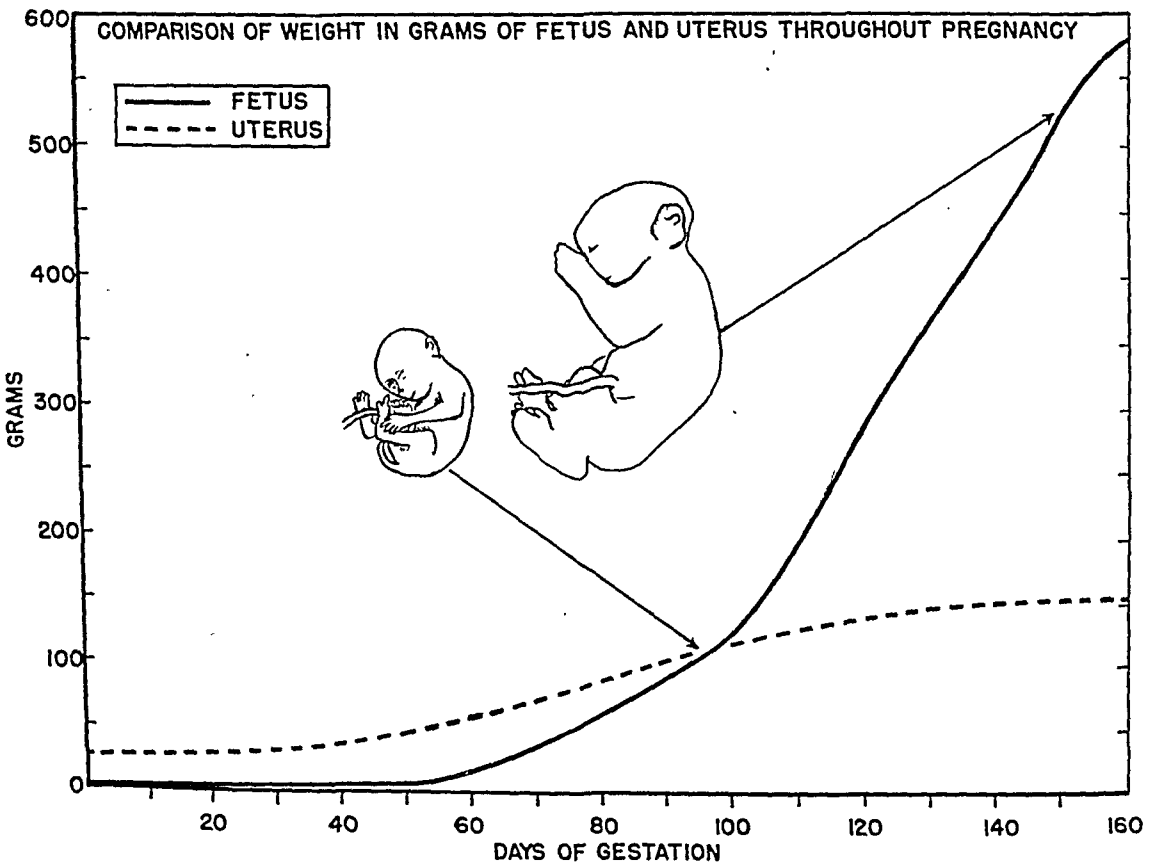


Fig. 4.—Fetal and uterine weight gain throughout pregnancy. Following the 100th day the curve of uterine weight gain levels off while that of fetal gain climbs rapidly. This illustrates the importance of the conversion period in maturation of the fetus. It further adds support to the belief that following conversion uterine enlargement is due to stretching rather than to growth of new tissue.

4. Supporting evidence consisting of changing vascular patterns and changing patterns of uterine weight gain and fetal growth is given.

5. This mechanism at once implies that the onset of labor is, in part at least, governed by the degree of uterine growth which occurs prior to conversion and that fetal maturity at birth is related to the length of the post-conversional phase. Further implications are possible.

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patterns of uterine growth, were enigmatical until the concept of rapid uterine elongation following conversion was elaborated on the basis of observations upon the rabbit.

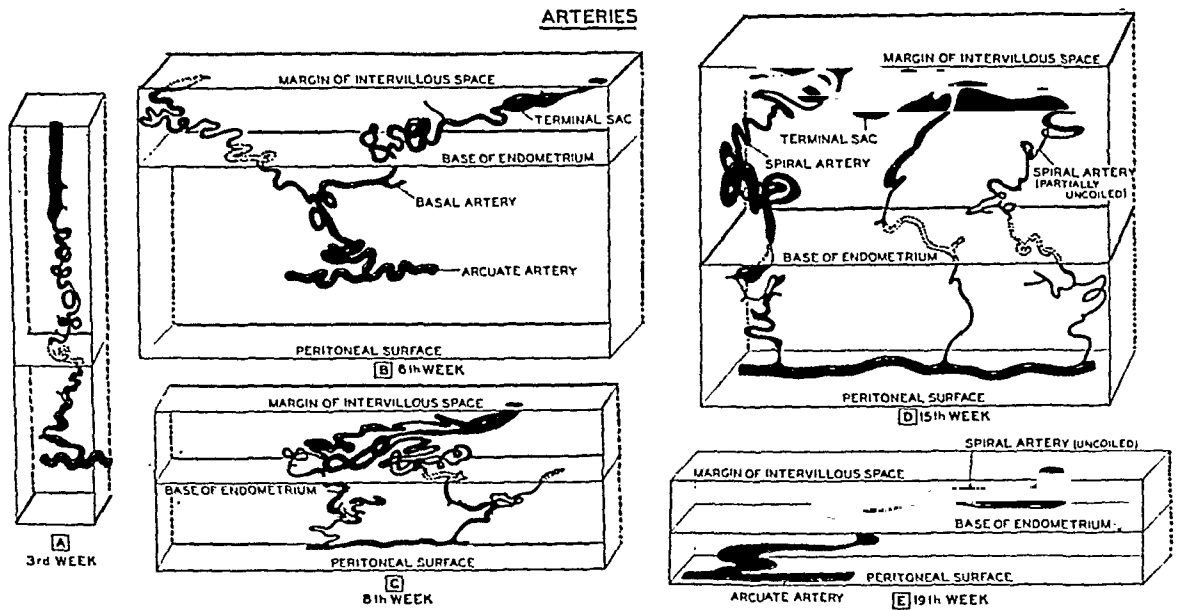


Fig. 5.—A composite diagram made from serial sections of the pregnant monkey uterus at various intervals during gestation. Note that following the 100th day the vessels of myometrium and endometrium which were previously coiled have become straightened and elongated. All sections taken at placental site (From Ramsey.<sup>13</sup>)

The foregoing résumé correlates several separate observations. It supports the view that, in the process of uterine accommodation of the conceptus, several distinguishable physiological states exist, following in order. It implies that after conversion, uterine growth diminishes greatly and stretching begins, thereby possibly influencing the length of gestation. Further, it shows that absolute fetal growth is much greater following conversion, which means the fetus matures rapidly in this period. It is most important in terms of fetal maturity, then, that no interruption or shortening of the postconversion phase takes place. The growth of a normal amount of uterine wall with normal vessels prior to conversion would seem to be important in assuring a normal postconversional period. This, and other methods of studying conversion, a critical point in the growth of uterus and welfare of fetus, are at present being applied to the human being by one of us (E. C. G.) and will be reported upon at a later date.

### Summary

1. The concept of uterine accommodation of the products of conception is briefly stated.
2. A method of analysis used in examining soft tissue x-rays of the gravid rhesus monkey uterus is given.
3. Results of these analyses suggest that on or shortly after the 100th day of gestation an important change in the pattern of uterine growth occurs. This consists of a relatively rapid elongation from a spherical to a cylindrical organ.



3. Fobe, 1940: Patient aged 23 years. Uterine curettage and round ligament suspension were soon followed by pregnancy, and then spontaneous abortion at three months. Eighteen months later while in the third month of the second pregnancy there was slight bleeding from an elevation the size of a hazelnut on the anterior cervical lip. This was excised and was diagnosed endometrioma with deciduel reaction. The pregnancy was undisturbed.

4. Henriques, 1941: Patient aged 40 years. Nine deliveries with the last one eight years before. A soft, bleeding mass the size of a hen's egg, which proved to be a hyperplastic endometrial growth, was removed from the vaginal portion of the cervix. The cervix was then amputated.

5. Hobbs and Lazar, 1941: White woman, 40 years old. There had been full-term deliveries twelve and fourteen years before, and nine years ago uterine suspension, bilateral salpingectomy, and left oophorectomy. Panhysterectomy was performed for menorrhagia. In addition to fibroids of the uterus, there was a small papillary body in the cervical canal near the external os which showed typical endometrial glands imbedded in stroma.

6. Lash and Rappaport, 1943: White woman, 31 years old. Full-term deliveries in 1926 and 1928, and two induced abortions. Slight vaginal bleeding at times for three years ceased after a small, dark red area was removed from the anterior lip of the cervix. This proved to be endometrial tissue partly covered by stratified squamous epithelium. The patient was well eighteen months later.

Lash and Rappaport proposed certain criteria favoring a diagnosis of primary endometriosis of the cervix. These have been altered and abbreviated as follows: (1) localization of the lesions on the anterior cervical lip or to one side of the external os; (2) an island of endometrial glands on the vaginal portion of the cervix, beneath the stratified squamous epithelium or exposed on the surface; (3) an endometrial island lying in scar tissue; (4) absence of evidence of extension from endometriosis involving the uterus, rectovaginal septum, or vaginal wall; (5) cessation of symptoms after eradication of the lesion.

The five cases we have to report are as follows:

CASE 1.—R. G., a white woman, was 35 years of age in 1939 when endometriosis of the cervix was discovered. She had had full-term deliveries in 1928 and 1931, and in 1937 uterine curettage was performed with removal of a uterine polyp. In 1939 curettage was done for incomplete abortion. Two slightly raised, round, purplish areas were seen on the anterior cervical lip to either side of the midline and in locations which could have represented the sites of tenaculum punctures at the first curettage. Both lesions were removed and gave the same microscopic picture of typical decidual reaction of stroma and glands covered over by the cervical squamous epithelium (Fig. 1). In February, 1948, panhysterectomy was done for increasing menorrhagia. In addition to multiple leiomyofibromas of the uterus, there was one small area of adenomyosis of the uterine wall. There was no suggestion that this isolated lesion could have had anything to do with the endometriosis of the cervix nine years before.

CASE 2.—A. A. was a white woman, 37 years old. She had a low forceps delivery in 1943 after a 3 cm. obliquely right and anterior incision of the elongated anterior lip of the cervix. Eight weeks later cervicitis was treated by cauterization. Examination in 1946 because of slight vaginal bleeding showed a small, bright red, slightly raised, round lesion just to the right of the external os and in the scar resulting from the incision of the cervix. The lesion was removed and the site thoroughly cauterized. Microscopic examination showed a nest of typical endometrial glands and stroma beneath the stratified squamous epithelium.

## PRIMARY ENDOMETRIOSIS OF THE VAGINAL PORTION OF THE CERVIX UTERI

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*(From Harper Hospital and Wayne University College of Medicine)*

WITH one possible exception (Novak), references indicate that primary growth of ectopic endometrium on the uterine cervix is very rare. Most lesions of the cervix are obviously secondary to endometriosis of the recto-vaginal septum. Extension from the uterine corpus is also mentioned, though we have never seen such an instance. Likewise to be excluded is so-called adenomyosis of the cervix (cervical gland endometriosis, or cervicosis) as described by Teacher and further studied by von Torzay-Kiss, Salles, and others. This condition consists of more or less questionable invasion of cervical stroma by glands which are cervical in origin, or possibly from remnants of the mesonephros, and definitely not endometrial. Also not to be included are decidua-like changes of the cervical mucosa associated with pregnancy. There is little evidence here of glandular structure but rather surface changes which are largely stromal in appearance. In several cases examined after pregnancy, there was no suggestion of endometriosis.

We have been able to discover reports of only six cases of primary endometriosis of the cervix in a rather thorough review of the literature. Although Novak stated that he had "... seen a number of instances of endometriosis of the cervix uteri," it was not clear whether or not he was referring to primary involvement. In the last nine years we have found four certain or probable instances in our practices, and another probable one among the clinic patients at Harper Hospital. In addition to the question of the frequency of primary endometriosis of the cervix, the condition is of interest in regard to its etiology, and also because of its resemblance to carcinoma.

Essential points in the case reports found in the literature follow:

1. Fels, 1928: Nullipara, aged 33 years. History of uterine curettage in 1920, an attack of salpingitis in 1924, and abdominal suspension of the uterus in March, 1927. Six months later from a scar on the left side of the cervix were excised three red, lentil-sized nodules which proved to be typical endometriosis.

2. Rushmore, 1931: Patient's age, 26 years. Delivery in 1927 was followed by severe hemorrhage from a laceration beneath the urethra. Appendectomy and right salpingectomy in 1930. In 1931 a polypoid nodule from the right side of the external cervical os showed typical decidua lying beneath the stratified squamous epithelium. Later a uterine curettage yielded tissues of a normal pregnancy, and laparotomy showed essentially normal pelvic organs.

CASE 3.—T. C. was a white woman, 25 years old. The first pregnancy in 1942 ended in spontaneous abortion at three months. She had a full-term delivery in 1943, with cautery treatment of cervicitis afterward. Three years later an examination because of right lower abdominal quadrant pain showed the uterus retrodisplaced with tenderness on the right side but no palpable enlargement of the adnexa. Just outside the external os and opposite each other on the anterior and posterior cervical lips were two red lesions about 5 mm. in diameter. These were removed and microscopically proved to be nests of typical endometrium beneath the squamous epithelium (Fig. 2). The next year there was another uneventful delivery. Subsequent examinations showed the uterine and adnexal findings as before.

CASE 4.—B. G. was a white woman, 38 years old. After the birth of her seventh child in 1946 she complained of urinary stress incontinence on straining and coughing. There had also been frequent though slight vaginal bleeding. In addition to vaginal outlet relaxation, there was a small, red, raised area on the anterior cervical lip. This lesion was removed and was found to consist of endometrial glands and stroma which were covered, except for a small part, by stratified squamous epithelium. This patient reportedly died in 1948 of breast carcinoma with widespread metastases.

CASE 5.—R. R. was a white woman, 31 years old, with deliveries in 1941, 1944, and December, 1946. About two years later she was examined because of slight bleeding for three to four days preceding menstrual periods. There were about a half a dozen purplish, punctate areas on the anterior cervical lip, of which three were removed. Microscopically these showed endometrial glands and stroma situated beneath the stratified squamous epithelium of the cervix.

Among these eleven reported cases there are four in which, because of operative inspection of the pelvic organs in two (Fels, Rushmore) and in two with the additional examination of the completely removed uterus (Hobbs and Lazar, and our first case), extension of endometriosis from other organs to the cervix can be ruled out. In five others (Fobe, Henriques, and our Cases 2, 4, and 5) the absence of anything pointing to involvement elsewhere makes primary cervical endometriosis highly probable. The case reported by Lash and Rappaport and our third one are more doubtful because of pelvic findings which could possibly have been due to endometriosis of the adnexa. It is interesting that in three instances (Fobe, Rushmore, and our first case) the endometrial transplants in the cervix had undergone decidual changes in response to pregnancy.

The etiology of endometriosis of the cervix is largely a matter of conjecture. The Müllerian source of the cervical mucosa has suggested the possibility of mutation into endometrium, but Hobbs and Lazar found no facts in support of this idea. A more likely origin appears to be transplantation of endometrium to the cervix, as occurs sometimes in the vagina and perineum. Fuchs successfully grafted endometrium from the supravaginally removed uterus to the remaining cervix. In view of the many injuries to the cervix by labor, abortion, infection, and operation, with the frequent presence of endometrial fragments, endometriosis of the cervix might be expected commonly. Apparently the cervix is generally unsuitable for the growth of endometrium. Hobbs and Lazar suggested vaginal acidity as the inhibiting factor. In support of the transplantation idea, it is significant that in the eleven reported cases there was without exception a history of labor or operation as a cause of a traumatic site for transplantation. Our first case strongly suggests implantation of endometrium in tenaculum punctures. In our second case and Fels's the endometriosis was situated in old scars.

Endometriosis of the cervix has some gross resemblance to carcinoma and also may cause abnormal bleeding. A positive diagnosis is made from examination of a biopsy specimen, and the lesion should then be eradicated

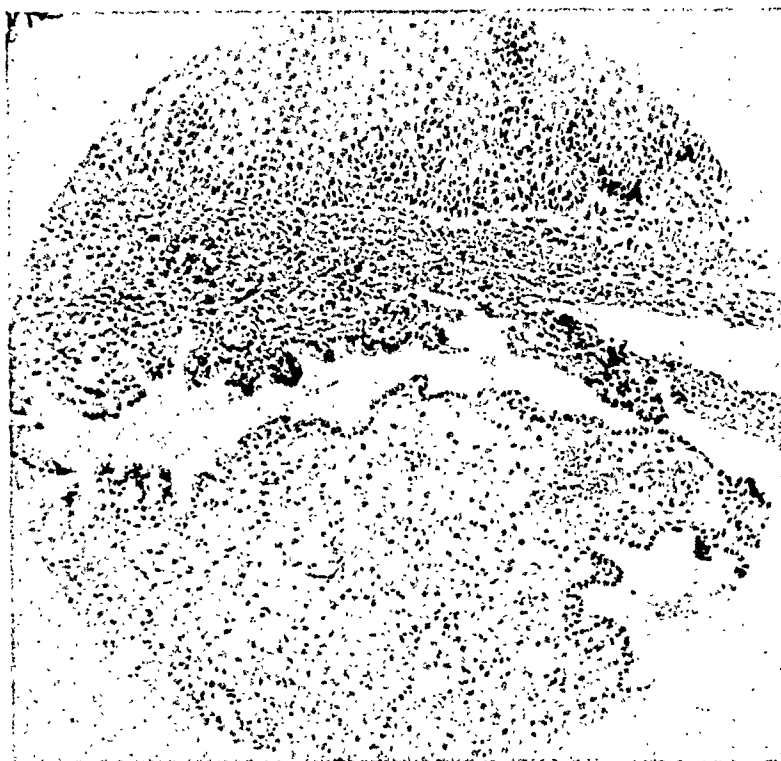


Fig. 1 (Case 1).—Pregnancy changes of glands and stroma in endometriosis of the cervix. Cervical squamous epithelium above.

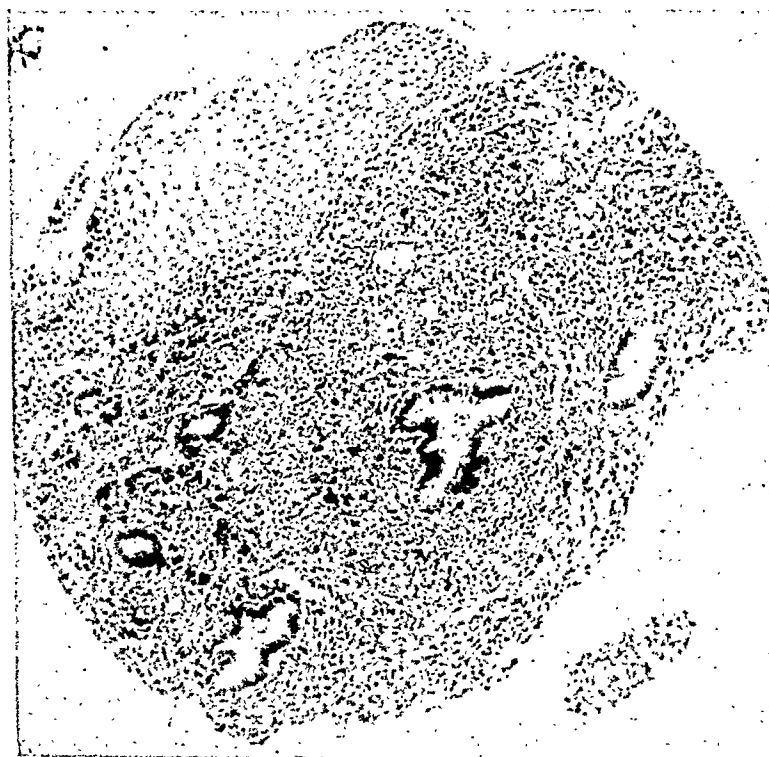


Fig. 2 (Case 3).—Glands and stroma of cervical endometriosis lying beneath the squamous epithelium covering.

## PREGNANCY ASSOCIATED WITH HYPERTENSION AND INTRACRANIAL HEMORRHAGE\*

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THE incidence of intracranial hemorrhage as a complication of pregnancy is infrequent and is generally thought to be a result of hypertension. A recent experience with this complication has led one of us (M. D. K.) to review the cases of all patients with cerebrovascular hemorrhage which occurred on the Obstetrical Service of the Morrisania City Hospital. Five such cases were found among 25,000 deliveries from 1930 to 1948, an incidence of one in 5,000 pregnancies. These cases are summarized as follows:

CASE 1.—Mrs. M. S., a 31-year-old gravida ii, para i, registered in the prenatal clinic on Aug. 11, 1947. Her last menstrual period occurred Jan. 20, 1947, and the estimated date of confinement was Oct. 27, 1947. Her history revealed the following: In 1945 she had a normal spontaneous delivery following which her blood pressure was 150/100 and remained elevated during the immediate postpartum period. At that time the Kahn test was positive (four plus). In January, 1946, she was admitted on the surgical service for a local swelling beneath the left jaw and the blood pressure was 150/100.

The prenatal examination revealed no physical abnormalities. She weighed 149½ pounds, the blood pressure was 142/90; the urine and Wassermann were negative. During her pregnancy she was given a salt-free diet for her hypertension. Her prenatal course was uneventful until Oct. 24, 1947, when she gained 8½ pounds between her regular fortnightly visits. The blood pressure was found to be 148/98 and the urine negative. Hospitalization was advised.

That day the membranes ruptured spontaneously and she returned to the hospital. On admission she was in labor; vertex presenting as right occipitotransverse; head engaged, cervix dilated 2½ fingers. A catheterized specimen of urine contained one plus albumin and occasional white blood cells; the specific gravity was 1.014. Her blood pressure was 168/110. She developed strong and frequent contractions and the following morning delivered spontaneously a living child. The blood pressure during labor was 185/108. Ten hours post partum she complained of severe pain in the back of her neck and around the shoulders. She vomited large quantities of undigested food and became very drowsy. The blood pressure was 220/130. A pre-eclamptic routine was instituted. For several days there was very little change in the clinical course. The blood pressure varied between 188/130 and 150/108. The urine showed two to three plus albuminuria. On Oct. 29, 1947, neck rigidity was noted, and the temperature had risen to 101° F. She was given penicillin. A neurological consultation was requested; the findings were marked nuchal rigidity, opisthotonus, and depressed but equal tendon reflexes, negative Kernigs, and no Babinski. The fundi showed slight blurring of both discs. The diagnosis was subarachnoid hemorrhage. Meningitis, bacterial or toxic, was considered as a second possibility. Lumbar puncture was performed and revealed an initial pressure of 320 mm. water; the final pressure was 115 mm. of water with an Ayala index of 3.6 per cent. Microscopic examination showed 1,870 white cells, of which 86 per cent were polymorphonuclear leucocytes; the red cells 125,000; the Wassermann, Kahn, and cultures were negative. Following the lumbar tap the headache was relieved for several hours. The blood pressure was 170/108. Intravenous glucose and magnesium sulfate were administered. Subsequent spinal taps showed a progressive decrease in pressure with gradual

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by the actual cautery or excision. Finally, should experience confirm our observations regarding the relative frequency of primary endometriosis of the cervix, the question must arise as to its possible role in the etiology of adenocarcinoma of the cervix.

### Summary

Although only six authentic or probable instances of primary endometriosis of the cervix were found in the literature, the fact that we were able to add five more suggests that the growth is not uncommon. The condition probably has its origin in the transplantation of fragments of endometrium to traumatized areas on the cervix. Clinically, the endometrial areas have some resemblance to carcinoma. A diagnosis can be readily made by microscopic examination of a tissue biopsy. The lesion may then be destroyed with the cautery or excised. The part played by endometriosis in the origin of adenocarcinoma of the cervix uteri is as yet purely speculative.

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the total proteins 36 mg. per cent. The smears were negative and the cultures showed no growth. No gross blood was noted. A catheterized specimen of urine contained one plus albumin with occasional white blood cells and 10 to 20 red cells. The temperature reached 102° F. A second spinal tap the next day revealed a cloudy fluid; the initial pressure was 252 mm. water with an Ayala index of 8.4 per cent. Spinal fluid chemistry showed sugar 3.1 mg. per cent, chlorides 789 mg. per cent, and protein 33.2 mg. per cent. Microscopic examination revealed many red blood cells, mostly crenated, indicating that the blood in the spinal fluid was not traumatic but due to bleeding into or from the meningeal spaces. At this time nuchal rigidity was noticed and the blood pressure was 190/130. Despite therapy the patient became progressively worse, developed a pulmonary edema, and expired on June 8, 1945, four days post partum.

*Summary and Comment.*—This multigravida with a hypertension during her first pregnancy that persisted between pregnancies, developed a pre-eclamptic toxemia between the thirty-first and thirty-third week of her current pregnancy, manifested by the appearance of a marked rise in blood pressure, albuminuria, and edema. During labor there was a further increase of 35 mm. Hg during the systolic phase and 20 mm. Hg during the diastolic phase.

Although her symptoms immediately post partum were indicative of intracranial complication, it was not suspected until she became stuporous and developed a hemiparesis fifteen hours after delivery.

This case illustrates, as does the preceding one, the presence of a superimposed toxemia in a patient with pregnancy vascular hypertension which terminated fatally from subarachnoid hemorrhage.

CASE 3.—Mrs. J. M., a 32-year-old white woman, gravida vi, para v, entered the hospital on July 19, 1939. Her chief complaints were headache, vertigo, spots before the eyes, and ankle edema of two months' duration. Her last menstrual period was Dec. 18, 1938. The expected date of confinement was Sept. 25, 1939. Previous history revealed that she had been delivered nine years ago in Malta at which time she had kidney disease with high blood pressure and hematuria.

On admission the blood pressure was 155/98 and there was moderate ankle edema. A catheterized specimen of urine contained a one plus albumin reaction with numerous hyaline and granular casts. The Fishberg concentration test showed a fixation of the specific gravity at 1.010. The blood chemistry revealed urea nitrogen 13.5 mg. per cent and the sugar 89 mg. per cent. With bed rest, restricted fluids, and salt-free diet, the headaches improved and the edema gradually diminished. On July 31, 1939, the headaches recurred and the blood pressure was 160/100. A twenty-four-hour urine specimen contained 3.4 Gm. albumin. A second blood chemistry revealed a uric acid of 8.8 mg. per cent, urea nitrogen 40 mg. per cent, and the serum protein 8.5 mg. per cent. In view of the evidence of increasing renal damage, it was decided to terminate the pregnancy. A medical induction of labor was tried but was unsuccessful. Catheters were then introduced into the uterus. After one-half hour of labor she complained of severe headache, had a convulsion, and became comatose. The blood pressure reading was 200/130. The spinal fluid was under increased pressure and grossly bloody. She died shortly thereafter, undelivered, without regaining consciousness. The diagnosis was subarachnoid hemorrhage.

*Summary and Comment.*—Previous history indicated that she had a nephritis associated with hematuria and hypertension during her first pregnancy. Aggravation of this kidney condition during her current pregnancy was manifested by a rise in blood pressure, particularly the diastolic; an increase in albuminuria and evidence of azotemia. This case terminated fatally not by uremia as would be expected but by intracranial hemorrhage.

CASE 4.—Mrs. M. T., a 40-year-old white woman, gravida v, para iv, was admitted to the Medical Service on Feb. 13, 1936, in a semiconscious state, restless with stertorous respirations and a paralysis involving the right side of the body. The following history was obtained from the husband. She was a known hypertensive and had a "stroke" eleven years ago. She was seven and one-half months pregnant and had had no prenatal care. Two weeks prior to admission she complained of headaches. Two hours before admission the headache became severe, she fell forward and lost consciousness.

disappearance of gross blood. The patient continued to improve and on the tenth day post partum showed only a slight stiffness of the neck. The blood pressure was 128/80. Ophthalmoscopic examination showed a moderately narrowed arterial tree with some increase in the light reflex indicative of pre-existing hypertension. She left the hospital against advice on the sixteenth postpartum day at which time her blood pressure was 136/84 and the urine continued to show a two plus albumin reaction.

Four and one-half months after delivery, she returned to the follow-up clinic. The pressure was 128/80; the urinalysis and blood chemistry were normal. The visual fields were within normal limits. The Kahn and Mazzini tests were reported as two plus. Neurological findings were considered normal.

*Summary and Comment.*—This multipara, a known hypertensive, developed signs of toxemia in the latter part of the second pregnancy manifested by elevation of blood pressure above the prepregnancy level, albuminuria, edema, and retinal changes indicative of hypertensive vascular disease.

The intracranial lesion which aggravated the symptoms was subarachnoid hemorrhage, proved by spinal tap. The symptoms of headache, vomiting, drowsiness, increased albuminuria, and elevated blood pressure were mistaken for impending eclampsia. Neurological examination revealed the true nature of the condition and proper therapy then hastened her recovery.

Despite the presence of an equivocal positive serology, syphilis was not considered the causative factor. It is known that syphilis is rarely the cause of subarachnoid hemorrhage, and intracranial aneurysms are practically never due to this disease. In fact, most of the cases of subarachnoid hemorrhage in syphilitics are due to a coincidental aneurysm or rupture of a vascular anomaly.

This case therefore illustrates the presence of a true toxemia (pre-eclampsia) engrafted upon a pregnancy hypertension, further complicated by subarachnoid hemorrhage, with resulting recovery.

CASE 2.—Mrs. L. M. J., a 23-year-old Negro gravida ii, para i, visited the prenatal clinic on April 4, 1945. Her last menstrual period was on Sept. 15, 1944. Her expected date of confinement was June 22, 1945. As a child she had malaria and typhoid fever but no kidney disease. Her previous pregnancy was associated with hypertension. A communication from Fordham Hospital where she was delivered in 1944 stated that she had had hypertension and had been treated for toxemia. Her sister who accompanied her explained that for the past one and one-half years she had had headaches, dizzy spells, and spots before the eyes and that she was under treatment by her family doctor for high blood pressure. Examination revealed a blood pressure of 130/84, a normal urine, and negative serology. General physical examination revealed no abnormalities. During her prenatal course there was a gradual rise in blood pressure until at the thirty-fifth week of her pregnancy the blood pressure was 150/100 and a faint trace of albumin was present in the urine. Hospitalization was advised.

She failed to enter the hospital until two weeks later. On admission she complained of occipital headaches, dizziness, spots before the eyes, and weakness. Examination revealed a full-term pregnancy with the vertex engaged. There was moderate ankle and hand edema. The blood pressure was 185/130. The eyegrounds showed a moderate degree of tortuosity of the retinal vessels. Laboratory findings were as follows: The urine had a specific gravity of 1.012, two plus albumin with occasional red and white cells. The blood chemistry showed a urea nitrogen of 9.5 mg. per cent and a uric acid of 3.3 mg. per cent. Magnesium sulfate was given intravenously for dehydration. The following morning labor started and she had strong uterine contractions. The blood pressure increased to 220/150. In the early part of the evening, June 4, 1945, she delivered spontaneously a living male child. Shortly afterward, she complained of severe headache, became very restless and uncooperative. Sedation was given. In the morning it was noted that she was semistuporous. Neurological consultation revealed a right hemiparesis, unequal pupils with the right larger than the left. There was forced conjugate deviation of the eyes to the right; meningeal signs were absent. A diagnosis of subarachnoid hemorrhage was made. Lumbar puncture revealed an initial pressure of 270 mm. water and contained chlorides 704 mg. per cent, sugar 59 mg. per cent and



reached 190/130. The reflexes were hyperactive; there was definite neck rigidity and evidence of right hemiparesis. The pupils were dilated (under mydriasis) and showed congestion; the discs were normal but small hemorrhages were seen in the right retina. The spinal fluid obtained by lumbar puncture was bloody and under increased pressure. The initial pressure was 15 mm. water and the final tap was 6 mm. water. The red cells were crenated, indicating a nontraumatic tap. The diagnosis was subarachnoid hemorrhage secondary to hypertensive vascular disease. The urine contained four plus albumin, many granular casts, few red cells and an occasional white cell. The urea nitrogen was 25 mg. per cent. Despite therapy the patient failed to improve; she developed pulmonary edema and expired on Feb. 29, 1936.

*Summary and Comment.*—This patient had a blood pressure of 140/90 before the twenty-fourth week of her pregnancy. A sustained pressure of 130 to 140 mm. Hg systolic and 85 to 90 mm. Hg diastolic during the early months of pregnancy is frequently indicative of pre-existing hypertensive disease.<sup>1</sup> The increase in blood pressure to 170/110 during the latter part of her pregnancy must be evaluated with the knowledge that nearly 40 per cent of patients with hypertensive disease show a rise of more than 20 mm. Hg over the blood pressure level of midpregnancy.<sup>2</sup> This fact makes the diagnosis of superimposed toxemia in a patient with hypertension often very difficult. However, in this patient the laboratory findings were more in accord with essential hypertension than with toxemia. Although cerebral hemorrhage may occur at any period in the course of essential hypertension, it is more frequent in those cases in which there are fluctuations in blood pressure.<sup>3</sup>

This case is considered one of essential hypertension aggravated by pregnancy which terminated fatally because of subarachnoid hemorrhage.

### Discussion

Of the five cases presented in this study, four died. Cerebrovascular accidents of such severity require careful analysis. In searching for factors which might play an important role in the sequence of events leading to intracranial hemorrhage, the following deserve special comment: (1) hypertension, (2) toxemia, (3) pregnancy and labor.

*The Role of Hypertension.*—Normal arteries can withstand very high pressures over very long periods of time without rupture.<sup>4</sup> When rhexis of a blood vessel does occur there must be underlying disease or a congenital anomaly of the vessel wall. In recent investigations on cadavers, it was found that even with pressure as high as 1,520 mm. Hg, Lampert and Mueller<sup>5</sup> were able to rupture the cerebral vessels in only two of the thirty cadavers, and both of these were in syphilitic individuals.

It is safe to presume that the patients in the cases presented above had some pre-existing lesion in the vascular system. All of the patients had a pre-existing hypertension. Three had essential hypertension, one had chronic nephritis, and the other, cardiovascular disease. Where fundoscopic examinations were made there was evidence of vascular changes reflecting similar pathology of the cerebrovascular system. These lesions, as stated above, predisposed such patients to a possible cerebral accident when the blood pressure increased beyond the level to which the vessel walls had been accustomed.

High blood pressure therefore may become a precipitating or contributing factor in intracranial hemorrhage if there exists some underlying pathology of the cerebral vessels.

*The Role of Toxemia.*—Toxemia of pregnancy either occurs in women who are otherwise normal or may be superimposed on patients with existing hypertension. Toxemia (nonconvulsive type) seldom causes cerebral accidents in those who are otherwise normal. This is not surprising in view of the fact that such toxemias are more common in women during their first pregnancies. Most primiparas are young, usually in their early twenties, with a normal vascular tree and free from previous hypertension. The hypertension

On admission the blood pressure was 170/110. There was no evidence of external injuries. She was seven and one-half months pregnant but no fetal heart tone was audible. There was evidence of right organic hemiplegia with a positive right Babinski; the reflexes on the right were increased and the abdominals on the same side were absent. There was two plus ankle edema. The heart showed definite enlargement. Examination of the eyes showed a drooping of the right lid; the pupils reacted to light; the optic discs were edematous, the edema extending to the surrounding retinal tissues. Hemorrhages and exudates were seen particularly in the neighborhood of the discs. The arteries were contracted; the veins dilated. Symmetrical colobomas were noted extending through the ciliary body and choroid but not through the optic nerve. Ophthalmoscopic diagnosis was hypertensive retinopathy with congenital colobomas of the uveal tract.

The pertinent laboratory findings were as follows: The Wassermann and Kahn were negative; the blood chemistry was within normal limits. The urine was reddish brown color, acid reaction with four plus albumin and containing numerous granular casts; there were 40 to 50 white cells. The spinal fluid was clear; the initial pressure was 208 mm. water; the final pressure was 95 mm. water. The protein was not increased; the sugar was faintly positive and microscopic examination showed 130 red blood cells. The smears and culture were negative. The clinical impression was (1) malignant phase of essential hypertension and (2) cerebral accident.

She remained on the medical service where therapy consisted of hypertonic glucose solution intravenously and sedation. The following day she continued to be restless, irrational, and comatose. The blood pressure was 170/120. The onset of labor was not noted because of her restlessness and stupor until she delivered a premature stillbirth in bed. The blood pressure had risen to 220/130. At this time she bled profusely per vaginam and was immediately transferred to the obstetrical service where a manual removal of the placenta was done and the uterus packed. Despite therapy she failed to improve, became cyanotic, and one hour after delivery expired.

*Summary and Comment.*—This case illustrates the effect of pregnancy in a patient with long-standing hypertensive cardiovascular disease. The history of a previous stroke was evidence of an existing severe intracranial vascular pathology which made the vessel wall increasingly susceptible to rhexis. The hypertension became clinically malignant resulting in a cerebral accident.

CASE 5.—Mrs. E. C., a 37-year-old white woman, gravida ii, para i, whose last menstrual period occurred on July 1, 1935, visited the prenatal clinic for the first time on Dec. 23, 1935. Her expected date of confinement was April 8, 1936. There was no history of renal disease. The blood pressure was 140/90. A voided specimen contained an occasional white blood cell. The blood count was 4.2 million red cells and the hemoglobin 80 per cent. The serology was negative. The blood chemistry and electrocardiogram were normal. Six weeks later because of headaches, ankle edema, and elevated blood pressure, she was referred to in the hospital from the prenatal clinic. On admission the blood pressure was 148/94. After several days she was discharged with a blood pressure of 140/80. It was believed that she had an essential hypertension.

On Feb. 25, 1936, she was readmitted because of vaginal bleeding of four days' duration. Moderate ankle edema was observed and the blood pressure was 170/110. Analysis of the urine revealed a trace of albumin, few hyaline casts with occasional white cells. Because of the vaginal bleeding she was typed, cross matched, and then examined vaginally (with the operating room set up for possible cesarean section). The cervix was two fingers dilated, the vertex presenting, and the margin of the placenta was palpated anteriorly and along the right edge of the cervix. A diagnosis of placenta previa was made. A No. 6 Voorhees bag was inserted extraovularly and a one-pound weight attached. After five hours of strong uterine contractions, the patient was fully dilated and expelled the bag. The blood pressure was 190/120. The membranes were then ruptured artificially and a living child was delivered by version and extraction.

One hour and forty minutes later the patient complained of severe pain in the head. The following day she was drowsy; the temperature was 102° F. and the blood pressure

Fluctuations in blood pressures occur during labor and especially during the second stage.<sup>4, 5</sup> In our small series the highest rise was obtained during labor; the systolic reached approximately 200 mm. Hg or more and the diastolic 120 mm. Hg or more. Although cerebral hemorrhage may occur at any period in the course of hypertension, it is more frequent where fluctuations in blood pressure exist. The variations in blood pressure before and during labor are shown in Fig. 1. Since it is apparent that fluctuations in blood pressure associated with labor may be a precipitating factor in vascular accidents, any measure which will avoid rises in pressure may prevent the development of this serious complication. These measures are: (1) the alleviation of painful stimuli by adequate sedation; (2) the relief of labor pains by proper anesthesia, i.e., caudal; (3) the elimination of the second stage of labor. In all hypertensives, regardless of cause, there should be a complete avoidance of all undue stress and strain.

The active treatment of cerebrovascular hemorrhage in pregnancy is lumbar puncture; additional measures are merely symptomatic. Prophylaxis offers the best hope for salvage of lives from this accident. Where evidence of chronic nephritis exists or where vascular pathology is evident, as in those with a previous intracranial accident, pregnancy should be avoided. Patients with essential hypertension may be permitted to become pregnant only in selected cases. The pregnancy must be carefully observed with proper regard for the increased incidence of toxemia and terminated as soon as untoward symptoms develop. On the other hand, if a patient with known hypertension had developed toxemia in a previous pregnancy, future pregnancies should be prohibited.

### Conclusions

1. Five cases of intracranial hemorrhage associated with pregnancy have been presented and discussed.

2. It is believed that a vascular lesion existing before pregnancy is the basis for such hemorrhage.

3. Labor and/or superimposed toxemia may be the precipitating factors because of the increased blood volume, the increased blood pressure, the fluctuations in pressure, and increased strain.

4. Adequate neurological examination or consultation in pregnant women with hypertension, albuminuria, and edema is advisable, especially in those with cerebral symptoms.

5. In those women with a past history of hemorrhage from rupture of an intracranial blood vessel, future pregnancies should be avoided. If intracranial hemorrhage complicates an early pregnancy, therapeutic abortion is advocated as soon as the patient's condition permits. If such patients are not seen until late in pregnancy then cesarean section is the procedure of choice.

We wish to thank Dr. A. B. Tamis and Dr. N. Savitsky for their valuable suggestions.

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in this type toxemia usually averages 140 to 170 systolic and 90 to 110 diastolic unless the condition is very severe. The hypertension is usually of short duration because patients with adequate care will be properly treated, and where treatment fails, the pregnancy is terminated. However, where toxemia complicates a pregnancy hypertension, the vessel spasm and its associated rise in blood pressure will add further strain to the vessel walls, predisposing them to rupture. This was the possible sequence of events in Cases 1 and 2. The existence of toxemia in such pregnancy undoubtedly speeds up the normal progressive changes of hypertension.

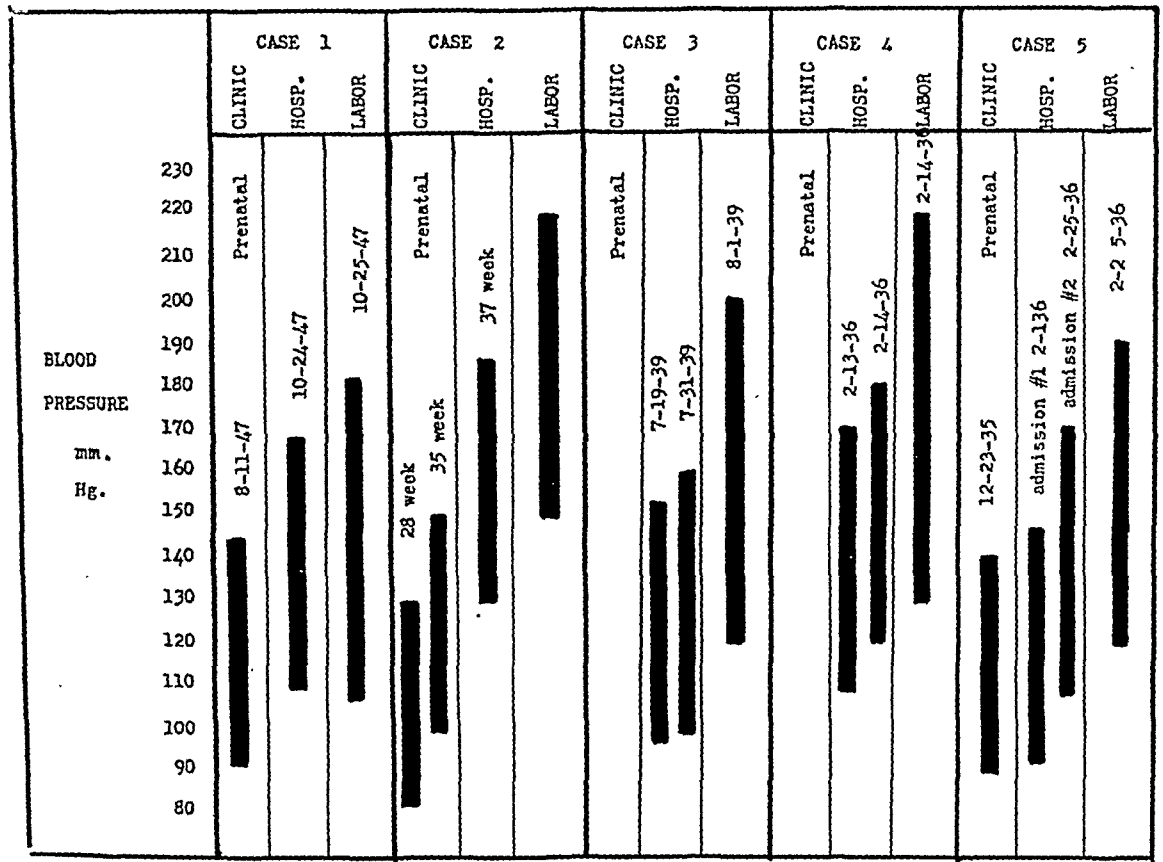


FIG 1. VARIATIONS IN BLOOD PRESSURE IN PREGNANCY AND LABOR

Cerebrovascular hemorrhage in pregnant women with hypertension often passes unrecognized. This is particularly true in patients with pre-existing hypertension and coexisting toxemia, since their combined effects are cumulative particularly with reference to the central nervous system. The headaches, drowsiness, hypertension, and increasing albuminuria are attributed to an aggravation of the toxemia or of the pre-existing hypertension rather than to the vascular accident, thus causing the true nature of the lesion to be overlooked. This was illustrated in Cases 1 and 2. It should be emphasized that adequate neurological examination must be performed and repeated if necessary in all pregnant women with hypertension who show aggravation of their cerebral symptoms, and especially in those with superimposed toxemia, if one is to recognize this complication and institute proper therapy. Lumbar puncture may often be necessary to determine the true situation.

*The Role of Pregnancy and Labor.*—All the patients were seven and one-half months pregnant or more at the time of the cerebrovascular accident. It is known that during this phase of pregnancy the increased blood volume and circulating load exert their greatest strain on the cardiovascular system.

Various theories as to the pathogenesis of cervical decidual islands have been proposed. Schock indicates that decidua may be brought down to the cervix during curettage. This theory is difficult to accept when one finds no history of either trauma or curettage in an individual patient. Frankl has indicated that an inflammatory stimulus is the principal predisposing factor. Meyer has modified this theory to indicate that decidual nests are found in the presence of local inflammatory irritation in a normal physiologic tissue which must have a certain innate pre-existing structure before decidual cells can be formed there. This opinion is strengthened when one finds that the decidual reaction in cervical polyps is very much more extensive and better developed than in the cervix proper.<sup>7</sup>

Grossly the lesions produced by decidual reaction of the cervix vary somewhat in character, although in general the appearance is very similar. This reaction in our cases was manifest as multiple, small, yellowish or reddish elevations varying from 0.5 to 2.0 cm. in diameter on the cervical mucosa. They were extremely soft, quite friable, and bled easily with slight trauma. These may be present as discrete nodules which vary in number or in form or as a raised plaque which covers portions of both the anterior and posterior lip of the cervix. The most severe lesion in our series was one in which the entire anterior lip of the cervix was composed of a very large fungating mass of tissue which displaced much of the cervix.

Microscopically the superficial epithelium is extremely thin and may even be partially eroded. The lesions are extremely vascular and are characterized in the typical late stages by decidual cells which are large, prominent, rounded cells often polygonal in shape. The cytoplasm is generally basophilic in color, is abundant, is occasionally vacuolated and is finely granular. The nuclei are relatively small, rounded, vesicular and some possess small nucleoli. In occasional areas the decidual cells are separated by edema (Figs. 2, 3, 4). Focal inflammatory reactions, characterized by collections of lymphocytes and occasionally polymorphonuclear leucocytes are pronounced in some instances while in others the tissue surrounding the nests of decidual cells is quite normal in appearance except for a moderate edema and vascular dilatation. Except for the increased numbers and dilatation, the vascular channels are normal in appearance as are the lymphatic channels.

As we trace the typical decidual reaction backward to its beginning it is noted that the cells progressively become smaller in size, and eventually one finds that the cells are those of the mesenchyme composing the stroma of the cervix. The initial lesion, then, is one in which there is an edema with separation of the stroma fibers and swelling of the individual cells (Fig. 1). This reaction is noted first beneath the squamous epithelium or in the stroma immediately surrounding the glandular elements. The cervical glandular elements which are enclosed in the sheets of decidual cells are often distorted and are lined by flattened cuboidal epithelium. This marked distortion of the cervical glands may produce a picture suggesting endometrial glands. However, on careful search a transition to cervical glands can be found. The absence of

## OBSERVATIONS ON THE DECIDUAL REACTION OF THE CERVIX DURING PREGNANCY

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IN THE cervix during pregnancy two distinct changes occur. One involves the epithelium, which exhibits very marked proliferative activity,<sup>1, 4</sup> and the other is a reaction which involves isolated patches of mesenchymal cells to produce a decidual type pattern.<sup>6, 7, 10, 11, 13</sup>

The epithelial proliferative activity includes a marked increase in the size and tortuosity of the glandular elements and epithelial proliferation both of the cuboidal cells of the glands and the superficial squamous epithelium covering the cervix. The glands tend to be dilated and are filled with mucus. The proliferation may be so extreme as to form polyps or masses which appear occasionally as condylomatous tumors. The cervical epithelial hyperplasias of pregnancy have been divided into three types.<sup>1</sup> Type One is characterized by simple hyperplasia of the squamous epithelium, formation of large rete cones, presence of long narrow papillae, and increased frequency of epithelial mitosis; Type Two by epithelial cells which appear to be arranged around the papillary stalks, and prominent epithelial masses which are two or three times as thick as in Type One; and Type Three by papillary growths or condylomatous masses composed microscopically of large simple stalks with a multitude of papillary side branches covered with thick squamous epithelium.

The second change is less well known. This change, involving the stroma, is composed of an alteration of the mesenchymal cells to a decidual type cell. This type of change may occur early in pregnancy<sup>7</sup> although apparently it is more frequent at term and subsides with no notable complications following termination of pregnancy.<sup>3, 5</sup>

It becomes clinically important to distinguish the decidual reaction of the cervix during pregnancy from carcinoma, which it grossly resembles, because of the obvious difference in the prognosis in these two lesions and, further, the presence of decidual reactions may explain the tendency to bleeding in the early months of pregnancy and occasionally at term. Pathologically, it is important properly to diagnose this reaction because of its relation to pregnancy and to enable us to define truly the source of bleeding if such should occur. Willer mentioned that if the decidual reaction is in the lower two-thirds of the cervix it is considered to be ectopic decidual. Other authors, however, feel that the decidual reaction is a part of the general change of pregnancy and is not to be considered as an ectopic type of reaction.<sup>10</sup>

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any marked evidences of inflammation suggest that inflammation is not necessarily a predisposing factor in the production of the decidual reaction in the cervix. Decidual reactions may also be seen in chronically infected tissue as was true in those of our three cases of decidual reaction which occurred in endocervical polyps.

The absence of endometrial glandular elements in our tissues indicate that ectopic endometrium is not necessarily present, although one would anticipate a decidual change in the uncommon case of cervical endometriosis. These changes appear to be more intense as pregnancy progresses. This indicates that the same pregnancy hormone effect which is operative in endometrial decidual change probably exerts a similar effect on the mesenchymal cells in the stroma.

Material

Our material for this study consisted of two sources of specimens. The first included ten pregnant or postpartum uteri from which sections of the cervix were available. Of these, seven were obtained at necropsy and three from uteri removed surgically for other lesions. In this group there were eight pregnant and two postpartum uteri. The postpartum uteri were three weeks and three months, respectively, post partum. There was no decidual reaction in either. Of the eight pregnant uteri four had and four did not have any evidences of a decidual reaction. Of the four with no decidual reaction only one was a term delivery. The other deliveries were at 12, 26, and 32 weeks, respectively. Of the four patients with cervical decidual reaction two were at term and the other two were at one and three months' gestation, respectively. The ages of the women were 23, 25, 36, and 38 years. From this small group no conclusions can be drawn but trends can be noted. It seems significant that 50 per cent had a decidual reaction, none had evidence of endometriosis, or severe infection of the cervix, and that neither of the postpartum uteri had a decidual reaction suggesting that this reaction resolves with no demonstrable sequelae.

Our second source of material consisted of sixteen cervical biopsies in which a decidual reaction was present. Eight of these specimens were collected from our own material over a relatively short period of time and eight were loaned to us by Dr. D. C. Beaver, Pathologist, Women's Hospital, Detroit.

In this series of sixteen cases the period of gestation at the time of biopsy was known in eleven. These were distributed as follows:

TABLE I. PERIOD OF GESTATION AT WHICH BIOPSY WAS TAKEN

PERIOD	NUMBER
2 months	4
3 months	1
4 months	2
5 months	2
Term	2
Total	11

It is significant that four were diagnosed at two months' gestation. Of these four there was a history of vaginal bleeding in two and no available information in the remaining two. In regard to the parity, there is no apparent significance. The age was known in twelve cases and the average was slightly

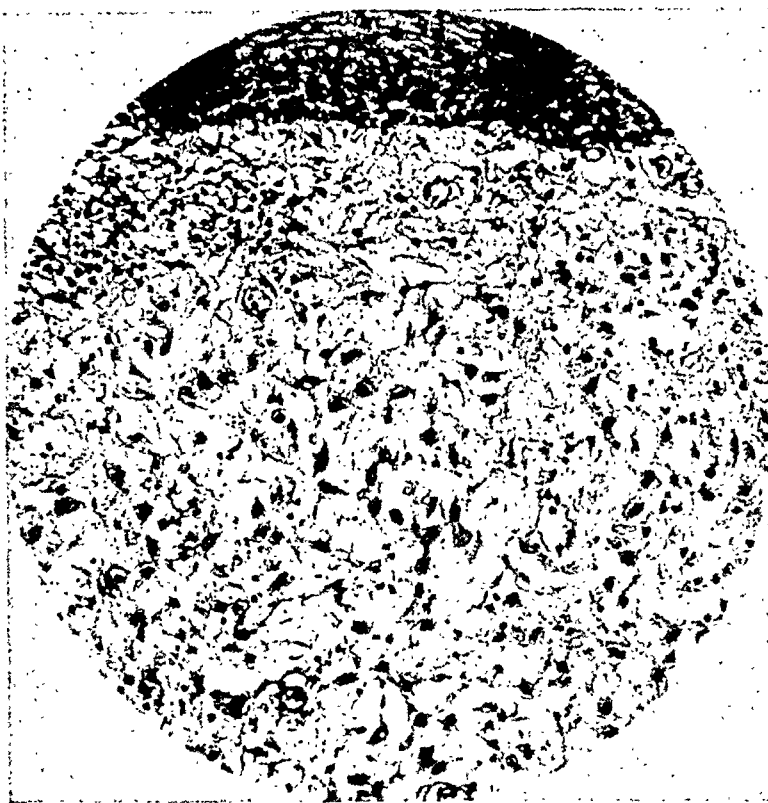


Fig. 1 (Case 2).—Intercellular edema with separation of stroma cells, swelling of cytoplasm, and tendency of the cells to become more round. ( $\times 275$ .)

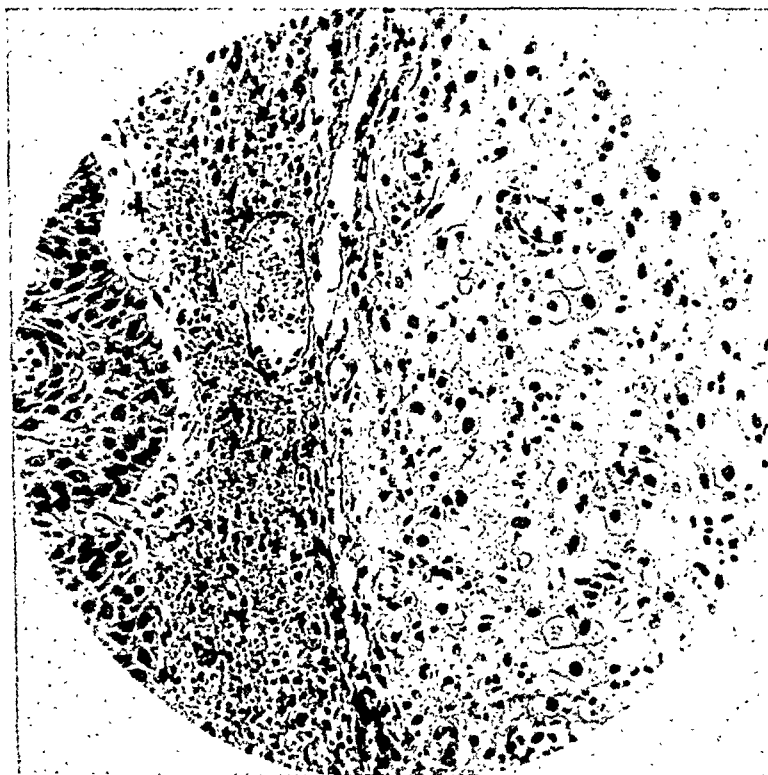


Fig. 2 (Case 6).—Further swelling of stroma cells accompanied by superficial squamous hyperplasia and increased vascularity. ( $\times 275$ .)



over thirty years which is a higher average age than we find in our routine delivery series (22 to 25 years in 1,441 deliveries of a recent four-month series). In eleven of the cases the outcome of the pregnancy was known. Of these, three aborted at variable periods from two to three months' gestation, while the other eight were term pregnancies. In this connection it is interesting to note that the cases reported by Klein and Domeier, Hennessy, and by Waldstein, all were term or approximately term pregnancies. This suggests that bleeding in early pregnancy caused by cervical decidual reaction is not invariably accompanied by abortion. In five of the sixteen cases there was definite knowledge as to the presence of vaginal bleeding, and vaginal bleeding was noted early in pregnancy in two of these, while the third had excessive vaginal bleeding at the time of birth of the child. In six cases the postpartum examinations which were done indicated that there was a complete resolution of the lesion following the termination of pregnancy. This is further borne out by our experience with the control material cited above.

### Summary and Conclusions

1. Decidual reactions of the cervix in pregnant women occur frequently and occasionally may account for bleeding during the early part of pregnancy and further may progress to such a degree as to produce significant bleeding at or near term.

2. Decidual reactions of the cervix are probably associated with the usual hormones of pregnancy and are not necessarily associated with either inflammation or endometriosis.

3. An awareness of this reaction on the part of the obstetrician and the pathologist may enable us properly to evaluate these patients.

4. There appear to be no permanent alterations of the cervix associated with this decidual reaction.

TABLE II. SUMMARY OF CASES WITH CERVICAL DECIDUAL REACTIONS

CASE	BIOPSY AT	PARITY	AGE	DELIVERY	COMMENTS
1	3 mo.	i	31	Term pregnancy	Irregular vaginal bleeding 6 weeks normal.
2	4 mo.	i	33	Term pregnancy	6 weeks normal.
3	5 mo.	ii	33	Term pregnancy	Follow up normal, no symptoms.
4		i	17	Term pregnancy	
5	2 mo.	i	23	Incomplete abortion	Profuse vaginal bleeding, one month.
6	2 mo.	iii	36	Incomplete abortion, 2 months	
7	Term	ii	31	Term pregnancy	
8	Term	v	28	Term pregnancy	
9	2 mo.	ii	29	Aborted at 3 months	Intermittent spotting 5 days; had subsequent dilatation and curettage; prior examination negative; follow up negative.
10	5 mo.	ii	36	Term pregnancy	6 weeks normal, no symptoms.
11	2 mo.	i	33	Term pregnancy	6 weeks normal.
12				No information	Polyp.
13				No information	
14				No information	
15	4 mo.	iii	32	No information	Polyp.
16				No information	



Fig. 3 (Case 4).—Small, well-localized clump of decidual cells. ( $\times 275$ .)

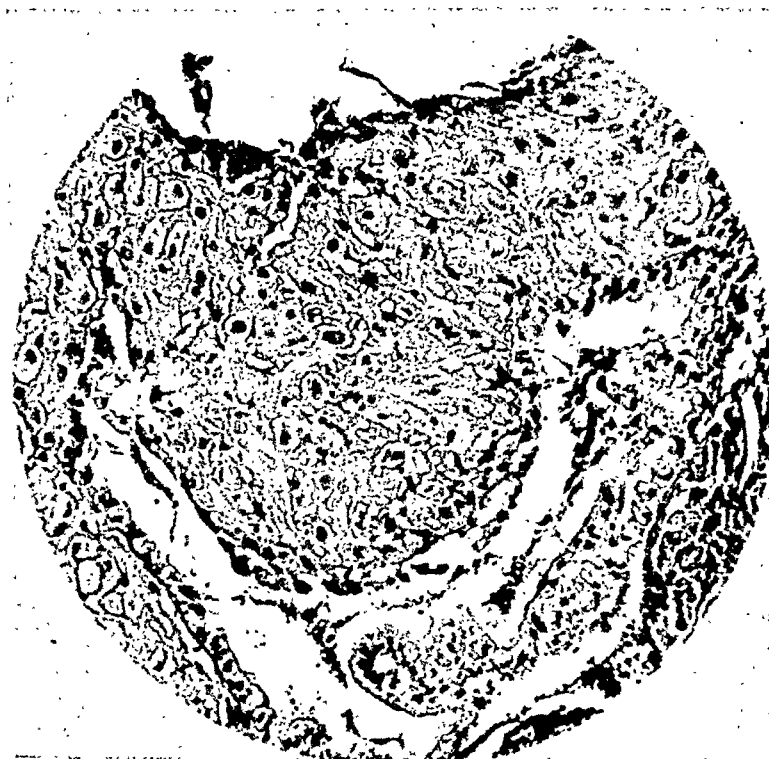


Fig. 4 (Case 15).—Masses of decidual cells arranged in subepithelial and periglandular areas. The gland epithelium is flattened and often distorted or partially lost. ( $\times 275$ .)

## PYOMETRA: A CLINICAL AND PATHOLOGIC STUDY\*

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PYOMETRA was first recognized more than one hundred years ago when one of the first cases was reported by Clarke in 1851.<sup>1</sup> Fourteen additional reports appeared between then and 1920. About 1920, treatment of carcinoma of the uterine cervix by means of radiation therapy became fairly well established. Consequently, in the succeeding years numerous articles presented discussions and reports of the occurrence of pyometra as a result of obstruction of the uterine cervix by malignant growths, polyps, fibromyomas, calcareous concretions or fetal bones, and as a result of radiation therapy. Previous cautery, atrophy and stenosis of the cervix also were mentioned. Bland,<sup>2</sup> in 1929, noted that stenosis of the cervical canal was not necessarily present in all patients who developed pyometra. The condition has been noted when tumors were produced experimentally in animals. Two instances of pyometra in women occurred in association with the presence of excessive amounts of estrogens, one in the presence of granulosa-cell tumor and the other following the administration of large doses of estrogens. Investigation of the bacteria found in cases of pyometra was made by Carter<sup>3</sup> in 1942.

The records of 87 patients at the Mayo Clinic who developed pyometra, from 1917 through 1945, were available for study. The condition was found at operation in 46 instances, at necropsy in 6, and at diagnostic curettage in 25; in addition, 10 patients experienced the condition during, or shortly after, the administration of radium to the uterus.

The general clinical background of this group of patients will be presented first, followed by consideration of the pathologic aspects.

### Clinical Features

The incidence of pyometra is not high, the 87 cases discussed herein representing a little more than 1 in 10,000 female admissions to the Mayo Clinic. For the most part, patients with pyometra are of advanced age. The average age in cases reported in the literature was 53.2 years; however, our group averaged 58.1 years, the youngest being 23 and the oldest 88.

The majority of patients with pyometra have passed the menopause, as would be expected in this age group. The significance of the postmenopausal state has been considered by Meigs<sup>4</sup> and by Graham and Failla<sup>5</sup> who have pointed out that accompanying the advance of years the tone and contractility of the uterus dwindle so that it cannot empty itself. In 68 patients (78 per cent), the elapsed time since the last menstruation averaged 14.2 years, and, of these, 58

\*Abstract of thesis submitted by Dr. DeVoe to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Obstetrics and Gynecology.

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The results of physical examination, particularly of the abdomen and pelvis, were helpful in a number of instances. Of the 87 patients, sixteen were found to have tenderness in the lower part of the abdomen, one of whom had semi-rigidity of the abdominal wall. Palpation of a tumor through the abdominal wall was possible in three patients.

Pelvic examination was performed on 71 patients.\* The uterus was enlarged in eighteen patients and a pelvic tumor was described in six. A mass in one or both sides of the pelvis was thought to be present in thirteen patients. Thus, in 37, or 52 per cent, of the 71 patients, enlargement of the uterus or a mass was noted. The cervix was absent in three patients, a cervical erosion was present in ten, a cervical scar in two, and an atrophic cervix in nine; in one patient a stem pessary was found in place.

Pyometra was the preoperative diagnosis in 21 of 71 patients. In the other 50 patients the results of examination led to a preoperative diagnosis of a number of conditions which in turn led to procedures through which pyometra was discovered. A pelvic tumor was diagnosed eleven times, cancer of the cervix five times, fibromyoma twice, menstrual irregularity nineteen times, and cancer of the fundus four times. Thirty-five patients were listed as having infrequently occurring conditions. The list of antemortem diagnoses of the patients who came to necropsy contained none of gynecologic interest.

### Pathologic Features

Studies of the gross and microscopic features of pyometra were possible in 52 cases in which the uterus was removed surgically or at necropsy. The Fallopian tubes were not present in all instances. The findings with regard to those patients upon whom a dilatation and curettage were performed will be noted later. In all patients evidence of the presence of pus in the uterus was found at the time of operation by the surgeon or immediately thereafter by the surgical pathologist.

The uteri from these patients varied greatly in size. The average weight of 50 uteri was 114.9 Gm., the lightest being 30 Gm. and the heaviest 187 gm. Two uteri contained multiple massive fibromyomas and hence were not considered in establishing the average weight; they weighed 530 and 390 Gm., respectively. The thickness of the uteri as measured at the fundus averaged 1.21 cm.; the thickest uterus measured 3.0 cm. and the thinnest 0.2 cm.

Many times pyometra was accompanied by other uterine pathologic lesions in the 52 cases in which the uterus was removed surgically. In this group there were 21 instances of benign uterine lesions; of these lesions fibromyomas numbered fourteen (27 per cent), endometrial polyps five (10 per cent), and adenomyosis two (4 per cent). Malignant lesions were present in eleven uteri (21 per cent), eight of which were endometrial carcinomas, one an extensive multicentric squamous-cell epithelioma of the endometrium, one a squamous-cell epithelioma which arose in the cervix and which involved the entire uterus, and one a squamous-cell endometrial metaplastic lesion. Concurrent pathologic conditions in other organs were of infrequent occurrence. There was one adenocarcinoma of the stomach, one adenocarcinoma of the ileum, and one diverticulum of the colon.

The status of the endometrium in this group of 52 patients was variable. In accordance with the average age of this group, a large number, 34 (65 per cent) exhibited an atrophic endometrium. A smaller number had an active

\*Pelvic examination was not done on the six patients who came to necropsy nor on the ten patients in whom pyometra developed during the course of radium therapy. In the "broken-dose" method of radium administration the cervix is probed prior to each treatment. When these patients complain of abdominal pain or vaginal discharge, probing the cervical canal is done and the diagnosis confirmed.

had experienced a spontaneous menopause while in the remainder it followed surgical or radiologic procedures. One patient had been amenorrheic for 21 years after a premature permanent cessation of the menses at the age of 18. Nineteen patients had not experienced the menopause and of these, eight had menorrhagia or metrorrhagia and one had oligomenorrhea. Sixty-two patients had given birth to living children; twenty had never been pregnant and five had been pregnant once but had aborted.

Previous diseases which might be of significance rarely had been present. Six patients had experienced pelvic inflammatory disease, three cancer of the endometrium, and three vaginitis. Endometriosis, fibromyoma of the uterus, puerperal sepsis, and syphilis each appeared once in the past histories of this group.

The past surgical history contained certain items of more than passing interest. Gynecological operations in some form had been performed on 58 (67 per cent) of the 87 patients and surgical procedures involving the cervix in varying degrees had been performed on 23, or 26 per cent, of the 87 patients; these operations consisted of dilatation and curettage in twelve, cervical amputation in four, trachelorrhaphy in one, and minor procedures (cautery, biopsy, polypectomy) in six. Twenty-four patients had experienced some abdominal surgical procedures. A large number of procedures previously undertaken did not pertain to the pelvic viscera.

A significant number of these patients had been subjected to irradiation therapy. Indeed, pyometra is one of the complications which has plagued radium therapists from the beginning. Lammers<sup>6</sup> and Condamin<sup>7</sup> reported cases of this complication that occurred during the early experience in the treatment of cervical carcinoma with radium but maintained that radium was the best therapeutic agent. Pyometra developed in three of 116 patients treated by Gegouin<sup>8</sup> who expressed the belief that postirradiation stenosis of the cervical canal was the underlying factor. In sixteen of our patients who received previous irradiation therapy elsewhere, pyometra developed. It was difficult to ascertain, by the patient's account, the extent and direction of this treatment. In twelve, however, radium was placed in the cervix or uterine cavity in doses apparently ranging from a menopausal dose to "complete treatment." The pelvic organs of four patients were treated with roentgen rays. Ten additional patients underwent radium treatment at the clinic and pyometra developed during or shortly after treatment. In nine of these, treatment was for carcinoma of the cervix and in one it was administered to induce the menopause. In three of these women pyometra developed during treatment or less than a week after the last treatment and in seven it appeared from two to sixteen weeks subsequent to the final treatment.

The complaints and symptoms of these patients frequently appeared as a triad. Vaginal discharge was present in 42 patients, vaginal bleeding in 35, and abdominal pain in 40. Nine patients complained of a low back pain. Infertility, irregular menses, hot flushes, and rectal pain each were present once or twice. Many patients, of course, had no complaints referable to the pelvis. Vaginal discharge was present and described as foul in 24 cases, purulent in 23, bloody or bloody mixtures with other types in 16, and brown in 8. Discharges described as serous, profuse, green, irritating, and mucoid occurred infrequently. Fourteen patients had no discharge. Some patients had more than one type of discharge. Forty patients experienced abdominal pain. Twenty-two complained of lower abdominal pain, nine described menstrual-type pain and nine complained of pain in either the right or left lower quadrant. Relief of pain with the onset of vaginal discharge occurred in five patients.

The body temperature was above 99° F. in only 13 patients, the highest reading being 99.6° F.

and Gouzy<sup>20</sup> maintained that a closed cervix is not essential. A physiologic retention may occur and increasing pressure may force exit. Varying types of inflammation were present in the cervix; seventeen of the 52 patients had subacute purulent inflammation, nine no inflammation, eight subacute inflammation, six chronic inflammation, nine acute purulent inflammation, two chronic purulent cervicitis, and one tuberculous cervicitis.

The total number of Fallopian tubes present on the 38 uteri having tubes was 72. The types of inflammation present in the tubes were as follows: no inflammation in 31, acute purulent inflammation in 13, subacute purulent inflammation in 21, chronic inflammation in four, and tuberculous reaction in three. Considering the ease with which it is possible for some inflammatory conditions to ascend into the tubes one would expect that the tubes would have exhibited the same type of inflammation as did the endometrium. Such was not the case. The type of inflammation in the 72 tubes corresponded to that in the endometrium in 22 instances (31 per cent) and was different in 50 instances. The three tuberculous endometria were all associated with tuberculous salpingitis.

Of the 25 patients upon whom a dilatation of the cervix and curettage of the uterus were performed, sixteen had a nonpatent cervix and in nine the status of the cervix was not given. In twelve of these 25 cases tissue was available for microscopic study; it was found that there were six cervical epitheliomas, four carcinomas of the endometrium, and two instances of only a purulent endometritis.

### Summary and Conclusions

The clinical and pathologic aspects of pyometra were studied in 87 patients, and the uteri of 52 were available for examination.

The average age of this group of 87 patients was 58.1 years, and in 78 per cent the last menstrual period had occurred 14.2 years before the onset of pyometra.

Gynecologic operations in some form had been performed on 58 (67 per cent) of the 87 patients, and in 23 (26 per cent) of the 87, a surgical procedure had been performed on the cervix. Twenty-one per cent of 71 patients, exclusive of the six who came to necropsy and the ten who received radium treatment at the clinic, had received irradiation therapy previously. Seven patients gave a history of endometrial or cervical malignancy.

The most prominent symptoms of pyometra were vaginal discharge, vaginal bleeding, and abdominal pain. Pyometra was not accompanied by fever.

Fifty-two per cent of 71 patients had a pelvic mass of one kind or another and 12 (17 per cent) had suspicious lesions of the cervix.

In 30 per cent of the patients who were treated surgically, pyometra was diagnosed preoperatively and in the remainder treatment was given for conditions which led to the discovery of pyometra.

Lesions of the uterus most frequently accompanying pyometra in the 52 cases in which the uterus was removed surgically were fibromyoma in 27 per cent, carcinoma in 21 per cent, endometrial polyps in 10 per cent, and adenomyosis in 4 per cent.

The endometrium was atrophic in 65 per cent of 52 cases in which the uterus was removed surgically. The types of inflammation present in the endometrium were as follows: subacute purulent inflammation in 56 per cent, acute purulent inflammation in 19 per cent, and chronic tuberculous purulent inflammation in

endometrium, four showing a late proliferative phase, three an early proliferative phase, and one a late differentiative phase. In three patients an extensive necrosis of the endometrium was present. As mentioned before, there were eleven instances of endometrial involvement by a malignant process; in four of these the lesion was endometrial adenocarcinoma, Grade II; in three endometrial adenocarcinoma, Grade I, in one a diffuse squamous-cell epithelioma, Grade III; in one a diffuse squamous-cell epithelioma, Grade II; in one an adenocarcinoma, Grade III; and in one a multicentric Grade III squamous-cell epithelioma of the endometrium.

The type of inflammation in the endometrium varied. Pus, of course, was present in all. The criteria used for acute inflammation was the presence of polymorphonuclear leucocytes and edema in the endometrium. A predominance of plasma cells was the principal criterion in cases of subacute inflammation, although eosinophilic polymorphonuclear leucocytes were often found. The presence of plasma cells in the uterus<sup>9</sup> is regarded by some as being indicative of chronic inflammation. Lymphocytes were the predominant cells found by us in chronic inflammation. On the basis of the foregoing criteria, five of the 52 patients had an acute purulent type of inflammation, with five others demonstrating, in addition, necrosis, giving a total of ten patients (19 per cent) with this type of inflammation. Twenty-nine (56 per cent) had a subacute purulent inflammation and ten had a chronic purulent inflammation. Tuberculosis was found in three uteri; tubercles with epithelioid cells, giant cells, and lymphocytes were present. When tubercles were discovered, special stains to demonstrate the presence of acid-fast organisms were tried, but none were found. However, the configuration seen scarcely allowed any other decision to be made since other granulomatous lesions which might be confused are extremely rare in the endometrium.

The principal feature noted in the myometrium was the presence or absence of fibrous change. The occurrence of fibrosis in the myometrium as well as in the cervix has been dealt with by Puxeddu<sup>10</sup> and Meigs.<sup>4</sup> In our group of 52 cases, marked fibrosis was present in 39 (75 per cent) and absent in 13 (25 per cent). In one the myometrium was diffusely infiltrated by a Grade III squamous-cell epithelioma. The number of uteri that revealed the presence of inflammation in the myometrium was surprisingly small; inflammation was not present in 24 (46 per cent), in twelve subacute inflammation was found, and in seven chronic inflammation was present. Four patients were found to have a subacute purulent myometritis, two an acute inflammation, and three acute purulent myometritis.

Accumulation of pus occurred both in uteri with and in those without a patent cervix. Twenty-four of the 52 uteri had a nonpatent cervix while the balance were not obstructed. Fibrosis of the cervix as a part of the general process in the uterus during the involutional age was present in 32 patients to a marked extent and nine showed fibrosis plus cystic cervicitis, giving a total of 41 (79 per cent) with increased fibrosis. Closure of the cervix as a result of atrophy, fibrosis of the circular structure, and subsequent adhesion has been demonstrated by Liegner,<sup>11</sup> Aza,<sup>12</sup> Alamanni,<sup>13</sup> and others (Gegouin,<sup>8</sup> Graham and Failla<sup>5</sup> and Puxeddu<sup>10</sup>). Other conditions of interest in the cervix were that three cervices had been amputated (plus one which had been removed post-operatively from the specimen) because of marked atrophy subsequent to radium treatment and 3 were the site of a Grade III squamous-cell epithelioma in which blockage occurred. This phenomenon has been recorded by Galabin,<sup>14</sup> Lewers,<sup>15</sup> Tate,<sup>16</sup> Oberndorfer,<sup>17</sup> and Roberts,<sup>18</sup> all of whose reports were published in early years; however, this condition, common in the past, is not so frequent now. The mechanism whereby pyometra occurs in the presence of an apparently patent cervix is conjectural; however, Tate,<sup>16</sup> Bland,<sup>2</sup> Maurizio,<sup>19</sup> and Guilhem



## END RESULTS IN THE SURGICAL TREATMENT OF OVARIAN CANCER\*

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THIS article concerns the treatment of patients with ovarian cancer in Dallas, Texas, from Dec. 31, 1935, to Jan. 1, 1947. It shows that surgical attack of the disease was frequently done without regard for its pathology. The effect on end results is considered. The method of study used was the same as described in a previous report.<sup>5</sup> The survey was completed in May, 1948.

### Material

Records of 294 women with a histologic diagnosis of ovarian cancer, and 20 others with a feminizing tumor of the ovary were reviewed. The feminizing tumors were considered separately for the reason that it was usually impossible to ascertain histologically whether or not they were malignant. Clinically, several of them proved to be cancerous.

To evaluate treatment of ovarian cancer, the tumors were divided into four clinical groups according to the modification of Heyman's classification made by Kerr and Einstein.<sup>10</sup> Among Group I the primary tumor and all visible cancer tissue was excised. Among Group II part or all of the primary tumor was removed but in every instance either some tumor was left, there was ascites, or the tumor content was spilled during removal. Group III included cancers recurring after removal or after irradiation treatment and Group IV consisted of the inoperable tumors.

### Subjects

Two-thirds of the patients were residents of Dallas County. The other one-third lived outside of Dallas County and came from other parts of Texas, Arkansas, Oklahoma, New Mexico, and Louisiana to Dallas for treatment.

The age of the women with ovarian cancer ranged from 16 to 87, with an average of 50 years. Two-thirds of them were over 45. Twelve, or 4 per cent, were under 30 years old.

### Symptoms

The usual symptoms of ovarian malignancy were abdominal tumor and pain. The average delay from the onset of symptoms to the time a correct diagnosis was made averaged 8.5 months. There was no apparent relation between the duration of symptoms and the extent of the disease. It was impossible to ascertain the amount of delay attributable to patient and to doctor but most of it was believed the fault of the patient.

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\*Aided by a grant from the Texas Division of the American Cancer Society.

6 per cent. The myometrium was markedly fibrosed in 75 per cent of the 52 cases and the inflammation present in the endometrium did not gain access to the myometrium in 46 per cent of the uteri.

The cervix exhibited increased fibrosis in 79 per cent of the 52 patients. The cervical canals of 54 per cent of the uteri were patent and the type of inflammation present in the cervix was approximately the same as that present in the endometrium.

The Fallopian tubes showed all types of inflammation, the type being similar to that of the endometrium in 31 per cent of the cases. In 90 per cent the type of inflammation present in the right tube was similar to that in the left tube.

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TABLE III. TREATMENT

TREATMENT	NUMBER
Exploratory laparotomy and biopsy	68
Unilateral oophorectomy	51
Bilateral oophorectomy	44
Unilateral salpingo-oophorectomy	30
Type of surgical operation unspecified	30
Subtotal hysterectomy and bilateral salpingo-oophorectomy	25
Bilateral salpingectomy and unilateral oophorectomy	12
Total hysterectomy and bilateral salpingo-oophorectomy	7
Subtotal hysterectomy and unilateral salpingo-oophorectomy	7
Abdominal paracentesis	5
Subtotal hysterectomy, bilateral salpingectomy, and unilateral oophorectomy	3
Total hysterectomy and unilateral salpingo-oophorectomy	2
Unilateral oophorectomy and bilateral salpingectomy	2
Bilateral oophorectomy and unilateral salpingectomy	1
Total hysterectomy and unilateral oophorectomy	1
Subtotal hysterectomy and unilateral oophorectomy	1
Died without operation, autopsied	5
Total	294

### Survival Rates

The survival rates for the 80 per cent of patients traced with ovarian cancer are given in Table II in relationship to the modified Heyman Classification. Spill of the tumor during its removal apparently decreased the chance for survival. In other words, aspiration and deflation of a tumor to facilitate removal are condemned. All women with sarcoma, epidermoid carcinoma, Krukenberg tumor, and dysgerminoma of the ovary died in less than four years after diagnosis. Four of five women with ascites and nearly all with palpable implants in the cul-de-sac were dead or had a recurrence within two years after a diagnosis of cancer was made. Since there were few patients with any one grade of tumor treated by any one method, it was impossible to evaluate properly surgical and irradiation treatment.

### Complications

More than one-half of the patients with ovarian cancer had known complications secondary to the disease or treatment, Table IV. The majority of women with ascites had one or more paracenteses. Seventeen with metastases to the bowel ultimately had an intestinal obstruction necessitating surgical intervention.

TABLE IV. COMPLICATIONS

COMPLICATION	NO. CASES
Peritoneal metastases (56 with ascites)	105
Extension to bowel	46
To lymph nodes; cervical 7; inguinal 7; other 3	17
Pulmonary metastases	7
Metastases to bone	4
Metastases to abdominal scar	4
Urinary tract obstruction	4
Metastases to iliac vessels	4
Total	191*

\*Among 168 patients.

### Feminizing Tumors

Several women with feminizing tumors of the ovary noted abnormal vaginal bleeding for over one year and in a few instances for as long as five to ten years

Pathology

The majority of ovarian tumors were primary in the ovary. Less than 8 per cent were metastatic, arising in order of frequency from the endometrium, colon, stomach, sigmoid, kidney, and cervix. Three of seven Krukenberg tumors were primary in the stomach, while the origin of the other four was unknown.

The histologic types of ovarian cancer are given in Table I and the clinical grade among patients traced three and five years is shown in Table II. Note, the specific histologic type was frequently not given. Most of the cystic tumors contained papillations. Over one-half of the 90 patients subjected to bilateral oophorectomy had cancer in both ovaries. One-seventh of the 122 women with one or both Fallopian tubes excised had metastases to at least one tube. Over one-third of the 46 women hysterectomized had spread of the malignant tumor to the uterine wall or into the uterine lumen. One-sixth of all the patients had extrapelvic metastases, usually to the omentum, and in nearly one-third of the 187 laparotomized other than for biopsy, the cancer had broken through the ovarian capsule. Spill of the tumor contents occurred among one-ninth of the women oophorectomized. Possibly some of the recurrences in these patients can be attributed to this technical misadventure. Grossly, all of the cancer was removed in only one out of 21 women.

TABLE I. HISTOLOGIC TYPES OF OVARIAN CANCER AND FEMINIZING OVARIAN TUMORS

HISTOLOGY	NUMBER
Adenocarcinoma, variety unspecified	144
“Ovarian cancer” type unspecified	37
Pseudomucinous cystadenocarcinoma	35
Serous cystadenocarcinoma	27
Metastatic, exclusive of Krukenberg tumors	16
Other*	15
Feminizing (granulosa cell 18, theca cell 2)	20

\*Krukenberg 7, epidermoid 5, sarcoma 1, dysgerminoma 1, embryonal 1.

TABLE II. SURVIVAL RATES

CLINICAL GROUP	FIVE YEAR (1936-1941)			THREE YEAR (1942-1943)		
	TOTAL	NUMBER LIVING	PER CENT	TOTAL	NUMBER LIVING	PER CENT
I	20	15	80.0	12	10	84.4
II	45	5	11.1	31	4	12.9
III	3	2	66.6	1	0	0.0
IV	32	0	0.0	23	3	13.0
Unclassified	4	1	25.0	5	1	20.0
Total	108	23	21.3	74	18	24.4

Treatment

The various surgical measures used to treat ovarian cancer are given in Table III. Only seven women in the entire series of 294 received what may be adjudged an adequate operation for ovarian cancer. In other words, only one in 42 women had a known bilateral salpingo-oophorectomy and total hysterectomy! One in fourteen women was laparotomized for recurrence of the tumor, found usually in the remaining ovary. Where an ovarian tumor was excised and a few days later reported to be malignant, the abdomen was seldom reopened to remove the other adnexus and uterus. The omentum was seldom removed and then only partially.

Reliable information regarding irradiation was available for only about one-half of the patients. These received x-ray to the pelvis or abdomen postoperatively.

tumor from experimental animals results in an increased survival rate presumably due to reduction in the number of cells available for growth. They are of the opinion this principle holds clinically.

Clinically the problem commonly arises as to whether or not an ovarian tumor is of the physiologic or neoplastic variety. Movable, cystic tumors 5 to 6 cm. or less in diameter in patients in the reproductive period of life are usually physiologic cysts. However, such tumors bear watching and if they do not regress, or instead become larger, an exploratory laparotomy is indicated.<sup>19</sup>

The value of irradiation in the treatment of ovarian cancer is difficult to judge because reporting of data is not uniform.<sup>22</sup> It apparently cuts down the formation of ascites and slows the growth of implants. Given postoperatively, life is occasionally prolonged.<sup>1, 7, 8, 10, 16</sup> In selected studies, total hysterectomy and bilateral salpingo-oophorectomy combined with postoperative irradiation have effected five-year survival rates of 35 to 40 per cent. On the contrary, Martin<sup>13</sup> seriously questions the value of x-ray postoperatively to prolong life. Baer,<sup>2</sup> Parks,<sup>17</sup> and the writer have observed that preoperative irradiation, in a few instances, made inoperable ovarian tumors operable. Kerr and Einstein<sup>10</sup> rightly condemn this procedure unless a histologic diagnosis is made beforehand. To give x-ray solely on a clinical diagnosis too often leads to castration of the patient for a benign lesion.

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prior to institution of treatment. Originally some of these tumors were considered to be sarcomas but on further study they were interpreted to be granulosal cell tumors. There were isolated instances where these tumors metastasized to omentum, peritoneum, Fallopian tube, scalp, and bone marrow.

Approximately an equal number of women laparotomized for feminizing neoplasms had removal either of one or both ovaries. Postoperative irradiation was seldom used. Six of thirteen women traced were dead within seven years, and two of four patients under 30 years of age died of the disease. It was apparent that the surgical procedure of choice for the older women with feminizing tumors included total removal of the uterus, ovaries, and tubes. The justification for doing less radical procedures in young patients as recommended by Hodgson, Dockerty, and Mussey<sup>9</sup> is questioned because two of four women under 30 years old died of the disease.

### Comment

Undoubtedly the great waste of time from onset of first symptoms to beginning treatment, and the use of improper operative treatment contributed to poor end results. It was apparent that many physicians did not understand the pathology of the disease. For the foregoing reasons, a brief discussion of the pathology and treatment of ovarian cancer is given.

Many ovarian malignancies arise within previously benign neoplasms.<sup>19</sup> The onset of the malignant change is insidious, so that the tumor is usually in an advanced stage of growth before a diagnosis is made. Ovarian cancers not uncommonly involve both ovaries. The tumor usually spreads by direct extension to the peritoneum, omentum, or tube. Less often metastases occur to the Fallopian tube by the lymphatics or veins and then to the uterus.<sup>4, 11, 18, 22</sup> It is obvious that total hysterectomy and bilateral salpingo-oophorectomy are the minimum acceptable surgical procedure for operable ovarian cancer.<sup>1, 3, 4, 6, 8, 10, 14, 15, 16, 18, 21</sup> In addition, Meigs<sup>14</sup> and Pemberton<sup>18</sup> strongly advise removal of the omentum. To the contrary, Baer<sup>2</sup> opposes its removal routinely for the reason that once tumor has spread to omentum it usually has invaded other extragenital organs or the peritoneum. Death from ovarian cancer commonly results from intestinal obstruction produced by peritoneal implants or invasion of other viscera, not from omental metastases. As previously mentioned, aspiration of ovarian cysts decreases the survival rate and is, therefore, condemned. On the other hand, drainage of very large ovarian cysts may be the only possible method of permitting subsequent removal without patient fatality. If done, a small midline incision is made and aspiration done under direct vision. The trocar wound is closed with a purse-string suture to prevent leakage.<sup>20</sup>

The normal ovary is removed unnecessarily often. In contrast, this survey revealed a tendency to conserve ovarian tissue in the presence of a malignant tumor of the ovary. Such a policy should be considered only in a young patient where the involved ovary is a freely movable, small cystic mass.<sup>15</sup> On the contrary, Helsel<sup>8</sup> is of the opinion that age should not be a factor in the treatment of ovarian malignancy. Ordinarily, if an ovary is removed, especially in women of menopausal age, and found to contain cancer, it is negligence if the other ovary, tubes, and uterus are not removed within a few weeks.<sup>14, 15</sup> All tumors taken out singly should be opened at the operating table to determine if they are malignant before the abdomen is closed. If the surgeon feels unqualified to pass on the gross specimen, he should consult the hospital pathologist. When ovarian cancer is found, as much of the tumor as possible should be removed with due regard to the length of anesthesia, blood loss, and shock. The more cancerous tissue excised, the more favorable the outcome, particularly if roentgen treatment is to be used.<sup>6</sup> Maun and Dunning<sup>12</sup> state that removing a portion of a

temperatures were taken by each of these four subjects so as to compare this criterion of ovulation to the hyperemia test. In so far as could be determined all four subjects were clinically normal. Three had become successfully pregnant one or more times without difficulty in conception. The fourth subject was a 30-year-old nullipara whose menstrual cycle was regular and who presented a completely normal history.

In addition, data were obtained from three selected patients who were to be subjected to pelvic repair surgery of nonendocrine significance. The surgical procedures were timed to occur on the day after ovulation as judged by the sudden rise in basal body temperature. In these cases as many morning urine samples as possible, immediately preceding the supposed time of ovulation, were obtained and tested by the Farris technique. It is to be noted that in two of these three subjects a freshly ovulated follicle developing into a corpus luteum was found.

Examination of the data (Fig. 1) indicates that our experience with the method has not been encouraging. None of our subjects, with the possible exception of L. S., yielded a normal or near normal ovulatory pattern according to the specifications of Farris. If this test is in reality dependable, the only interpretation is that all our subjects were abnormal with respect to ovulatory pattern. This does not seem likely because, as mentioned above, all these women were gynecologically and endocrinologically normal in so far as could be judged clinically and by past performance. Certainly, in the two subjects whose ovaries contained newly developing corpora lutea, the Farris test did not yield a "normal" reaction.

In the light of our lack of success with this method it is pertinent critically to re-examine the claims of Farris. In his first paper<sup>1</sup> he reports that a positive response on less than 3 *successive days* is to be considered abnormal. Yet in his chart of 52 "normal" cycles, 19 show positive responses on 2 or *less consecutive days*. Likewise, 13 of the 36 "abnormal" cycles were positive on 2 consecutive days. It is difficult to perceive from the data how these 19 "normal" cycles differed from the 13 "abnormal" ones. Likewise, the reasons for the arbitrary three days (later revised to four days) of required positive reaction is not readily understandable, especially in view of the fact that Farris<sup>6</sup> has also obtained positive reactions with pre- and postcoital urines of men and of women not ovulating at the time of urine collection.

Farris<sup>1</sup> reports that of eleven women showing normal ovulatory patterns and artificially inseminated on the day indicated by the hyperemia test, eight became pregnant, a successful prediction in 73 per cent. In a subsequent report, however, Murphy and Farris<sup>4</sup> outline results obtained by coitus or by artificial insemination timed in accordance to the hyperemia test. Sixty-six attempts in thirty-three cycles of ten women are detailed. All ten subjects became pregnant, one of them twice, a total of eleven successful predictions. Actually, however, the proportion of successes was only 33 per cent since in only eleven of the thirty-three cycles did conception occur. It is presumed that these eleven successes include the eight mentioned in the earlier publication. It is also to be noted that in many of the test cycles, coitus was repeated on a number of successive days at approximately the middle of the cycle rather than on the one day predicted by the test. The percentage of successful conceptions, therefore, loses a large measure of its significance for with repeated coitus during each cycle a 33 per cent incidence is not strikingly higher than that obtained without prediction of ovulation by special methods.

Furthermore, the significance of five of the eleven successes appears to be doubtful due to extenuating circumstances such as the substitution of a sperm donor for an infertile husband (Case 1), repair of closed fimbria (Case 2),

## ON THE VALIDITY OF THE HYPEREMIA METHOD FOR DETERMINING OVULATION TIME IN WOMEN\*

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THE search for a simple and reliable means of determining the time of human ovulation has led to the proposal of a variety of techniques. "Mittelschmerz," spotting, gonadotrophin excretion, changes in electrical potential and in basal body temperature, vaginal smears, and endometrial biopsies have been among the criteria proposed. One of the most recent suggestions is that of Farris,<sup>1</sup> who has adapted a technique previously presented by others<sup>2, 3</sup> as a test for detection of early pregnancy. The test depends on determining the extent of the hyperemic response of the immature rat ovary two hours after injection of 2 ml. of morning urine. A positive indication of ovulation is defined on the basis of hyperemia of a specified degree and quality as determined by comparison of the test animal's ovaries to a standard color chart. It is further stated that in the normal reaction, the subject's urine must produce the hyperemic response for at least three successive days (later revised<sup>4</sup> to four or more days).

In the original report,<sup>1</sup> Farris states that by use of this method he has correctly predicted ovulation time in a number of women, the criterion for correctness of the prediction being conception resulting from timed coitus or artificial insemination. Furthermore, the prediction of the time of ovulation in seven monkeys has been verified<sup>5</sup> by finding the corpus luteum of ovulation at examination of the ovaries at laparotomy.

Because of the great potential value of the technique, an attempt has been made in this laboratory to evaluate the hyperemia test in the prediction of ovulation. The published technique<sup>1, 6</sup> was followed exactly except that for the examination of the ovaries of the test rats natural north light or light from a battery of fluorescent lamps was substituted for the special lamp suggested. The test ovaries were compared to the Munsell Color Chart as nearly as possible as described by Farris. In addition, positive and negative controls were included in each group of test animals. The negative controls consisted of un-injected rats of the same age (usually littermates) as those injected with test urines. The positive controls were similar rats injected with 2 ml. of urine collected from patients known to be in the first trimester of pregnancy.

The test urines were morning specimens furnished daily throughout a complete cycle by each of four normal women volunteers. Daily basal body

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fifteen failures in these two cases is lacking. Possible infertility of the husband due to previous coital attempts is suggested (but not proved) as the reason for five of the failures. No explanation at all is given for five other failures.

Thus, even the cases cited by Murphy and Farris do not all clearly support their thesis and the incidence of success based on the hyperemia test may actually be as low as 18 per cent or less.

Another puzzling aspect of the test which requires some thought is the statement that the cause of the "positive" hyperemia is the increased titer of urinary gonadotrophin immediately preceding ovulation. Farris presents no evidence which places the responsibility for the positive response on gonadotrophin but he does state that a positive response was obtained with 3 to 25 rat units of purified gonadotrophin. On the basis of these figures it may be calculated that at the time of ovulation a woman must excrete at least 1,500 to 12,500 rat units of gonadotrophin per 24 hours. This figure is enormously greater than any previously reported<sup>7, 8, 9, 10, and others</sup> and approaches more closely the values hitherto associated with early pregnancy. Indeed, if Farris is correct on this point we may discard as erroneous all hitherto reported figures for gonadotrophin excretion by nonpregnant women.

It is conceded that a criterion for determining human ovulatory time is difficult to establish. The only certain means of proof is by appropriately timed laparotomy with subsequent microscopic examination of the ovaries. Evidence based on fertile copulation or insemination is suggestive but not conclusive particularly when incidence of success is as low as 33 per cent. Furthermore, it must be borne in mind that nonovulation in the absence of the "positive" hyperemia test also still remains to be proved. Therefore, until more conclusive evidence is available, the Farris hyperemia test must remain as an interesting but unproved suggestion.

### Summary

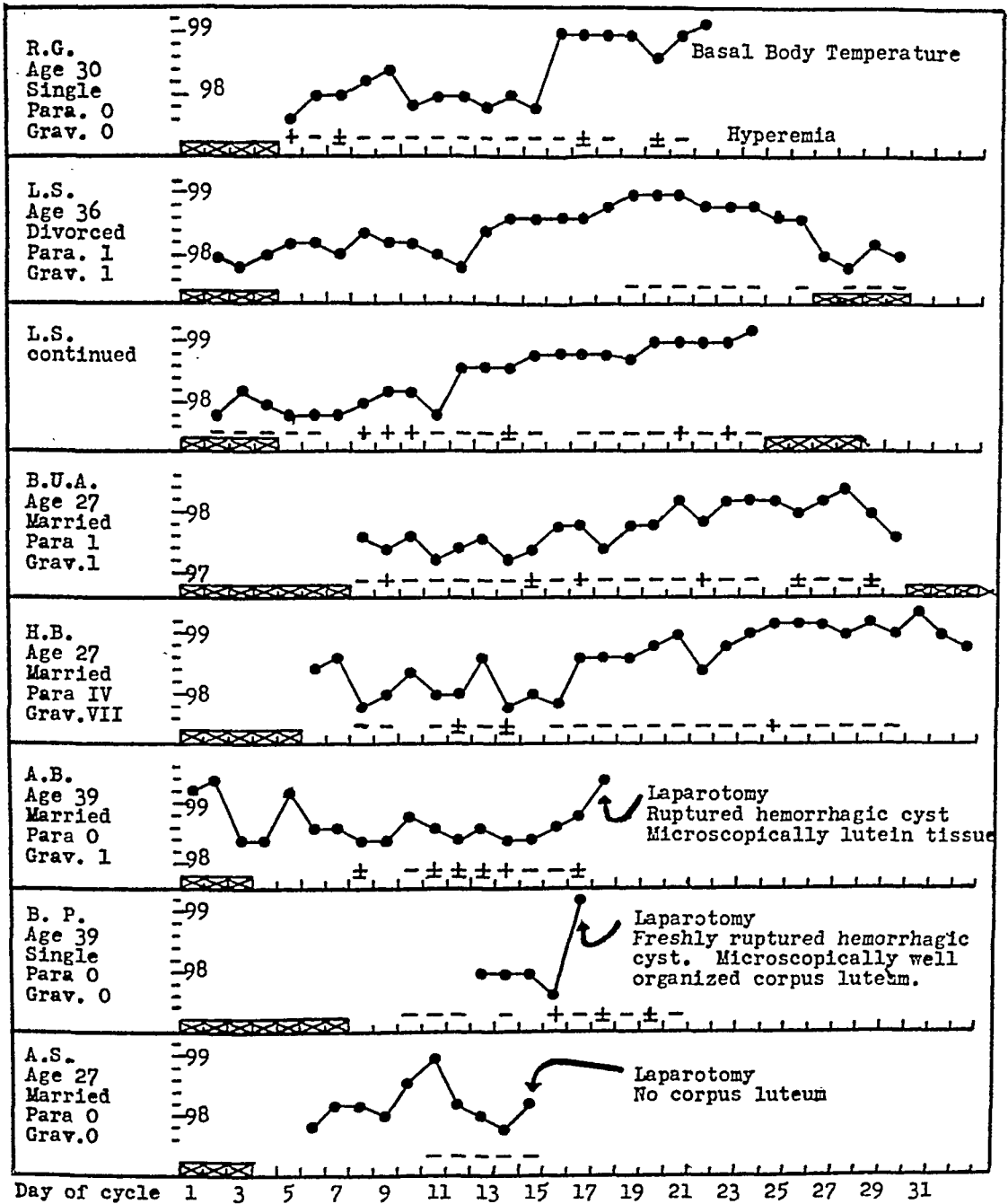
The Farris rat ovary hyperemia test for determination of time of human ovulation has been used in three human subjects followed by examination of the ovaries at laparotomy and in four subjects known from previous history to be fertile and gynecologically normal. In none of these was the specified "normal" hyperemia reaction obtained.

Certain flaws in the conclusions upon which the validity of the test is based are discussed.

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husband of doubtful or fluctuating fertility (Cases 4 and 6), coincident treatment of husband with gonadotrophic preparations (Case 6), and a relatively infertile husband plus suspected opening of a blocked tube (Case 10). Two other cases (5 and 7) had previously been pregnant and in these two cases, three pregnancies resulted from four coital attempts.



-, ± and +, respectively, refer to negative, doubtful and positive hyperemia response

Fig. 1.

Cases 4 and 10 are of further interest. These two subjects practiced coitus during seventeen cycles as advised on the basis of the ovulation test. During the final cycle in each case conception occurred. Adequate explanation for the

were concluded by outlet forceps after rotation of the head was complete. Patients were eliminated from the study in whom unanticipated obstetric difficulties were encountered which could influence the initial breathing time (difficult outlet forceps, prolonged second stage, evidence on postdelivery inspection of marginal separation of the placenta, etc.). It was felt that any other factors which might affect the initiation of respirations would be balanced by the size of the series, and under such controlled circumstances the most important single influence on the baby's crying time was the drug under study, an influence which was accentuated by using maximum doses throughout and by administering the drug just prior to delivery (one to two hours in most cases).

**Results.**—Three hundred eleven cases were found acceptable for study in this manner. These were divided into one hundred eighty-one patients who had received Nisentil and one hundred thirty patients who served as controls. The control cases were further subdivided into the following groups: 38 who received no medications, 32 who received Methadon, and 60 who received Demerol.

As revealed by the breathing and crying times, Nisentil is not a serious fetal depressant. Of the drugs tested, Methadon<sup>7</sup> produced a definite and at times very marked delay in fetal respiration, while Demerol and Nisentil both tended to approach the unmedicated group in promptness of breathing and crying. In two of the Nisentil cases, it was noted that after immediate establishment of breathing the babies became sleepy and required mild physical stimulation; both cases had received multiple doses of the drug. In general, however, little depressant effect could be traced to Nisentil used alone, and if administered two hours or more prior to delivery no significant effect at all was observed.

In an effort to determine what dosage level would be required to produce definite depression of the fetus, and to assess a cumulative effect, if any, disproportionately large amounts of Nisentil were administered to an additional group of thirty patients. Fetal respiratory depression became evident on the administration at regular two-hour intervals of five consecutive 40-mg. doses. That this amount would be required frequently is highly unlikely, but it may well indicate that, as is true with meperidine hydrochloride, continued administration throughout a protracted first stage could have a deleterious effect on fetal respirations.

### Discussion

It would be absurd to maintain that any systemic narcotic now known is totally without effect on the fetus. All have a depressant reaction of some degree, as any careful study will indicate. But it is possible to measure such depression, and to select drugs which will provide a maximum of pain relief for a minimum of depressant effect.

One of the benefits in this respect derived from Nisentil as we have used it has been the fact that when employed in 40 mg. doses concomitant medication with other drugs has become less necessary. Nembutal has rarely been indicated and if scopolamine has been employed its dosage has been low (0.2 mg.). The drug repeated at 2- to 2½-hour intervals has proved satisfactory to carry more than 90 per cent of these patients up to the time saddle block spinal has been established. There has been a significant freedom from side reactions, either observed at the time or reported subsequently.

### Conclusion

The hypodermic administration of Nisentil in 40 mg. doses provided adequate pain relief in over 90 per cent of the five hundred patients who received it during labor.

# THE OBSTETRIC USE AND EFFECT ON FETAL RESPIRATION OF NISENTIL

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THE substituted piperidene products have been thoroughly investigated as narcotic agents, and several modifications of the piperidene nucleus have been found highly satisfactory.<sup>1-6</sup> Since it is almost inevitable that any new pain-relieving drug which is introduced will be applied to obstetric analgesia, it becomes imperative to know the effect on the fetus of such drugs when administered during the course of labor. The present report records the effect on the fetal respirations of the 4-phenyl-4-acyloxy-piperidine, Nisentil\* administered to the mother prior to delivery, together with observations on its pain-relieving value in obstetrics.

## Procedure

Initial observations were carried out on five hundred patients to determine the proper dosage range for obstetric use and to evaluate the pain-relieving quality of the drug during labor. This evaluation was made by objective observation of the patient in labor and by postpartum questioning. In 40 mg. doses administered hypodermically, Nisentil has proved satisfactory for obstetric use. The duration of action of such a dose is about two hours, and characteristically the patients become drowsy, manifesting restlessness with each contraction. The progress of labor has not been significantly delayed. In a few women nystagmus has been noted, and mild mental confusion is not infrequent. Supplementary medication with the barbiturates or with scopolamine has been found to be necessary much less frequently, and in smaller doses. No untoward side reactions have been observed. Thirty-two of the five hundred patients were listed as receiving only moderate relief, seventeen "poor" to "none," while the remaining patients (90 per cent) were variously listed as having received "satisfactory," "good," or "excellent" results. The degree of pain relief was less than with 100 mg. of meperidine hydrochloride (Demerol) plus a barbiturate, and the amnesia was not as great as with meperidine hydrochloride and scopolamine combinations. Greater patient cooperation was retained, however, and over 70 per cent of these women were carried through the first stage in adequate comfort without additional medications.

## Fetal Respiratory Effect

*Method of Study.*—The time intervals between delivery of the head and (a) the first respiration and (b) the first lusty cry were carefully recorded, while an effort was made to eliminate or to standardize all factors other than the drug under study which might depress fetal respirations.<sup>7</sup> The pain of the labor was controlled either by caudal or by saddle block spinal anesthesia, obviating the use of systemic anesthetics or other analgesic drugs. All cases

\*Supplied by the Hoffman-LaRoche Company, Nutley, N. J.

## FATAL OBSTETRIC SHOCK FROM PULMONARY EMBOLI OF AMNIOTIC FLUID

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**I**N 1941 a series of eight cases of unexpected, sudden deaths in obstetric shock was described.<sup>1</sup> The necropsy finding common to all was the presence of numerous foreign bodies in the small pulmonary arteries, arterioles, and capillaries. These were regarded as emboli composed of the particulate components of amniotic fluid, including vernix caseosa (desquamated squamous epithelium and sebaceous material) and, in some cases, meconium (mucus and desquamated epithelial cells). Emboli composed of lanugo hair were later described.<sup>2</sup> These foreign materials were absent in the lungs of control interpartum cases. The clinical picture was that of sudden onset during labor or soon thereafter of strong or violent uterine contractions, restlessness, dyspnea, cough, rapid pulse, fall in blood pressure, cyanosis, etc., characteristic of shock. In four cases the pulmonary emboli were the most probable explanation for shock and death. In two cases there was, in addition, uterine hemorrhage and in two cases there were other important lesions as well.

It was possible to produce a similar clinical and pathological picture in rabbits and dogs by the intravenous injection of meconium and of unfiltered amniotic fluid, but not with filtered amniotic fluid. It is well known that in man and animals extensive showers of small particulate materials to the lungs can cause a shock reaction which may be fatal. This picture which is similar to if not identical with that of anaphylactoid shock is further characterized by widespread and, to a certain extent, species specific changes in the functional state of the smooth muscle of various body systems. It was believed that in some cases death was due to the pulmonary embolism. It was speculated that in other cases the state of shock might have caused uterine atony with resultant hemorrhage which together with the shock itself might have caused death. Finally, it was believed that the violent uterine contractions, which sometimes characterized the early stages of the condition, might have led to uterine rupture seen in one case, and in this way contributed, together with the shock of embolism, to death.

Later, two additional examples of the disease were described.<sup>2</sup> In these cases the embolism was not the cause of death, but they illustrated several additional features including the late histologic reaction to the emboli (previously seen only in the experimental animals), lanugo hair as emboli, and mild embolism in the absence of labor pains.

A number of confirmatory reports have since appeared. These include papers by Hemmings (one case), Goodof (one case), Gross and Benz (three cases), Wyatt and Goldenberg (one case), Jennings and Stofer (one case), Barron and co-workers (two cases), and Watkins (one case). Their clinical histories are typical and their photomicrographs illustrate the characteristic

Under carefully controlled conditions for study there was little evidence of fetal respiratory depression, and if the last dose was administered two hours or more prior to delivery, no significant effect on the fetus could be determined at all. Nisentil should prove a satisfactory adjunct to the armamentarium of pain-relieving drugs for obstetric use.

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about and within emboli. This is interpreted as signifying either that the mobilization of leucocytes is extraordinarily fast, or that the emboli enmesh leucocytes in passing through the blood, or that the embolism had preceded, at least in part, the clinical onset of symptoms by some time. At necropsy in this case a rare opportunity was overlooked to demonstrate the actual site of passage of the amniotic fluid from the membranes into the maternal circulation by special methods, using pressure and dyes. A rent was not visible on casual examination.

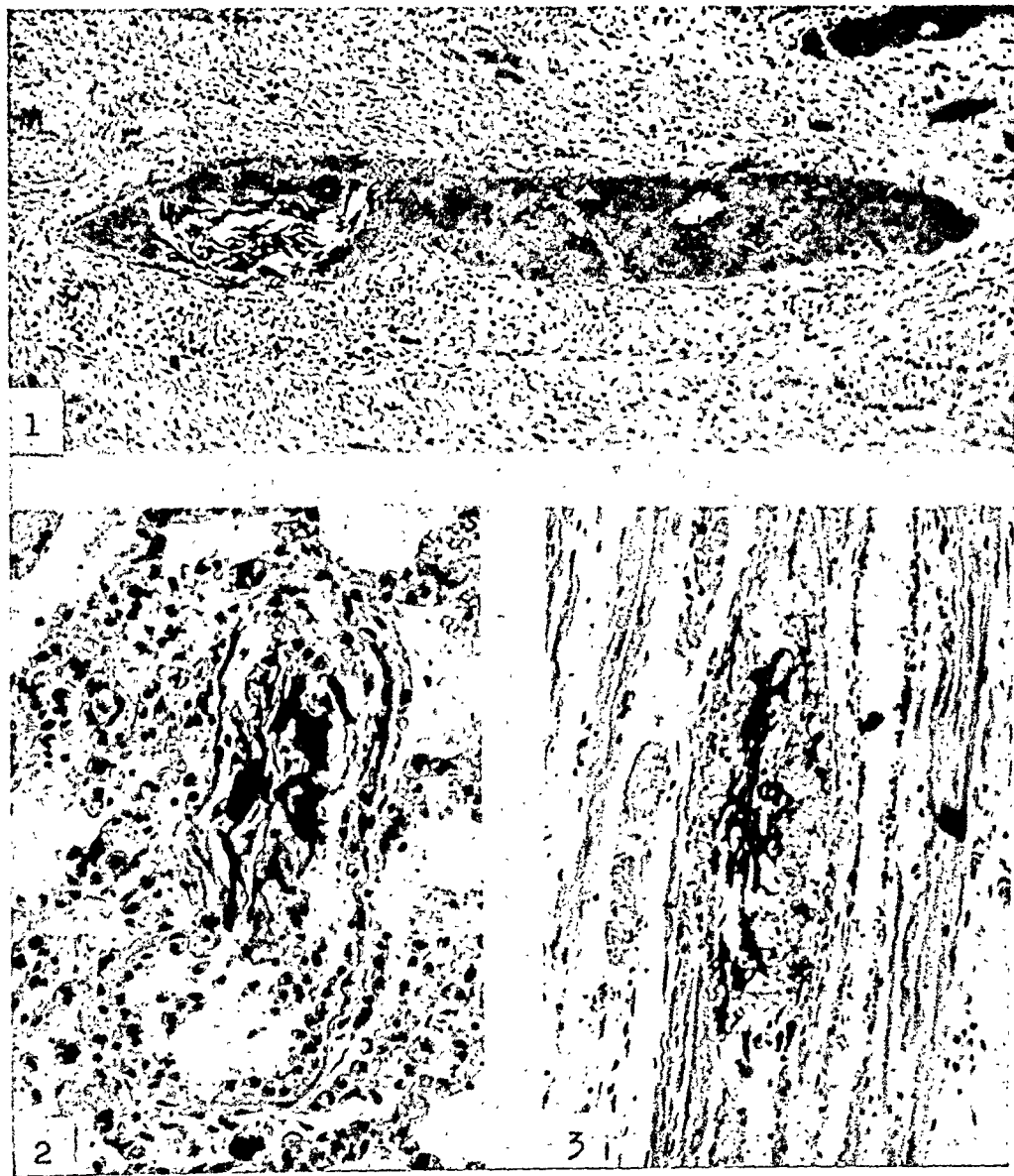


Fig. 1.—Uterine vein showing an embolus composed of epithelial squames, a little mucus, and sebaceous material at its left end. ( $\times 80$ .)

Fig. 2.—Dilated pulmonary arteriole filled by an embolus. It consists of epithelial squames enclosed by mucus which contains a few leucocytes (seen best at the lower end). ( $\times 250$ .)

Fig. 3.—Uterine vein showing an embolus of mixed composition but chiefly epithelial debris. ( $\times 140$ .)

emboli in pulmonary vessels. Jennings and Stofer have reviewed most of these cases. That they represent only a portion of the recognized cases is known to us as we have seen others in consultation, and there are references on record to cases which are incompletely reported such as that of Burt and of Nicholson. As was anticipated in the first paper, sublethal forms of what are probably this condition have been recognized pathologically,<sup>2</sup> and also clinically by Seltzer and Schuman and by us.

An outstanding new contribution was that of Gross and Benz who showed how the disease may sometimes be diagnosed in suspicious cases where necropsy examination is unobtainable by centrifugation of blood aspirated from the right ventricle. The embolic material, if present, separates as a special layer. Failure to find the emboli in the centrifugate would not exclude this diagnosis because the material might not have been present in heart blood at the moment that circulation stopped.

A new case which is perhaps the clearest and most dramatic in our series and which presents several new features is herewith presented. The time between clinical onset and death was exceedingly short (less than fifteen minutes). The membranes had not ruptured to the exterior. There was no hemorrhage whatever.

### Case Report

N. F. (No. 5772), a white woman, aged 44 years, was at term in her fourth pregnancy, which had been uneventful. She had had no symptoms suggestive of toxemia. The urine was free of albumin, the blood pressure had not been over 130 systolic, and the pulse was never counted over 76. Her youngest child was 19 years of age. After fourteen hours in mild to moderately severe labor the cervix was slightly dilated. The membranes had not ruptured. She was in good condition; she was up and walking around her room. Three minutes later she had a slight convulsion, turned cyanotic, and died within a few minutes despite measures for resuscitation, including Adrenalin, Coramine, and oxygen.

At necropsy, performed twelve hours after death by Dr. H. A. Frank, a normal term fetus weighing 3,320 grams was found within apparently intact membranes. The placenta was not detached. There was no evidence of hemorrhage, internal or external. The 310 gram heart showed dilatation of the right chambers. The lungs weighed 360 and 330 grams; they showed only a slight edema. There was no foreign body or other abnormality in the respiratory tract. The other viscera were essentially normal for a woman in late pregnancy.

The important microscopic findings were confined to the lungs and uterus. In addition to a slight pulmonary edema, bodies were found in many small pulmonary arteries, arterioles, and capillaries. They resembled epithelial squames, masses of mucus, masses of amorphous granular material resembling the sebaceous material in vernix caseosa, and leucocytes. These materials were found in the veins of the parauterine plexus and in the wall of the uterus itself (Figs. 1, 2, and 3).

### Comment

In many respects this case was typical of those previously described. An elderly multipara of short stocky habitus (length 5 feet, 1 inch; weight 157 pounds), after an uneventful pregnancy, suddenly and unexpectedly during labor went into collapse and died within fifteen minutes. The gross findings at necropsy were negative except for a dilated right heart and a slight pulmonary edema. All microscopic sections of lung taken at random, however, showed extensive embolization of small blood vessels by the particulate materials found in amniotic fluid.

The time which elapsed between the onset of symptoms and death, less than fifteen minutes, was the shortest in our experience, although others have reported such cases. Despite the short duration, however, there were many leucocytes



## WITHDRAWAL BLEEDING FOLLOWING HEXESTROL AND PREGNENINOLONE ORALLY

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IT IS a well-known fact that after the administration of estrogens in sufficient quantity to a patient with a normal uterus, withdrawal bleeding will occur. Several injections of hormone are used for this purpose. However, Zondek<sup>1, 2</sup> has shown that a strong injection containing estradiol benzoate (2.5 mg.) and progesterone (12.5 mg.), repeated in 48 hours, will usually cause uterine bleeding in a few days. Other investigators have noted that stilbestrol given orally can be used for the same purpose.

The oral use of stilbestrol produces satisfactory withdrawal bleeding, but a large percentage of the patients are nauseated when enough of this substance is given to cause a good flow of blood at a predictable time of onset. Hexestrol causes less nausea than stilbestrol,<sup>3-5</sup> but it is unlikely to produce uterine bleeding in the 1 mg. to 3 mg. daily doses commonly used for therapy of climacteric symptoms.

Because a more satisfactory type of oral therapy was sought, a woman with amenorrhea was given twenty-day courses of hexestrol using larger daily doses during each course. In this manner it was determined that 27 mg. or more daily always caused a light flow of blood lasting four or five days. It was decided to give this treatment to a series of patients to work out the details of a satisfactory method of administration, to determine the percentage of nausea, and to note what beneficial effects were produced. Later pregnenolone was added because hexestrol caused proliferation of the endometrium but no progestational changes.

Obviously, with this treatment there is relief of any estrogen deficiency symptoms and some help to the patient psychologically. Are there any organic benefits? A partial answer to this question is given in the discussion.

In the past, estrogen or pregnenolone has been given to many patients for various purposes.<sup>6-12</sup> Hexestrol has frequently been given for climacteric symptoms.<sup>13-23</sup> Cinberg has used stilbestrol and pregnenolone orally in the treatment of functional amenorrhea.<sup>24</sup>

### Method of Administration

Hexestrol\* was administered in 3 mg. tablets in three or four doses daily. The total amount given daily ranged from 9 mg. to 48 mg. Each original course of treatment lasted twenty days. On succeeding months the medication was usually taken from the fourth to the twenty-fourth days of the cycle so that bleeding occurred about every twenty-eight days. If it occurred

\*The hexestrol tablets were obtained from The Wm. S. Merrell Company of Cincinnati, Ohio.

In a previous publication the incidence of this form of obstetrical death was estimated to be about 1 in 8,000 confinements. This figure was based on the observation of three cases in the first 24,000 deliveries at the new Chicago Lying-in Hospital. This figure is probably too high because at that hospital since the time of making the estimation given here, there have been no further cases in over 26,000 additional deliveries. The case reported here came from another hospital. The exact incidence is hard to determine because the cases may occur at irregular intervals as witness the three seen by Gross and Benz within one year.

We stated that in our material this was the commonest cause of death during labor or in the first few hours of the puerperium.<sup>1</sup> In view of these observations it is difficult to understand the statement of Sheehan who in 147 deaths from obstetrical shock in a period of ten years recognized no examples of this condition. He stated that sections of lungs which he examined showed no emboli of amniotic fluid but failed to state how many lungs he had adequately examined. The experience of Scott who in eighty-two obstetrical deaths did not see this condition is also difficult to explain other than on the probable basis of failure to make the necessary histological examination of the lungs. In Feeney's learned lecture on shock in obstetrics there is no mention of cases due to this form of embolism although his second class is probably of this type. Johnson, in an excellent discussion of sudden death in obstetrics, fails to mention the possibility of this form of embolism; a review of microscopic sections of lungs in some of his obscure cases would probably disclose the characteristic emboli.

Fatal maternal embolism by the particulate contents of amniotic fluid is now a well-established cause of death. Because this label could be used to mask the cause of many types of unexpected death in parturition, this diagnosis should be accepted only when verified by the finding of particulate amniotic contents in the heart or lungs either by cardiac puncture or necropsy. On the other hand, in all obstetrical cases ending fatally in obscure shock in or shortly after parturition, this condition should be considered and searched for. The warning of Eastman is well taken. The diagnosis is easy if sections of lung are available. A death verified as from this cause cannot conceivably be considered the result of poor obstetrics. The condition should not be overdiagnosed but neither should it be underdiagnosed; it should stand on its proper scientific merits.

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There was a distinct psychological advantage from the production of bleeding, and several patients stated that they felt more like they had before the onset of the amenorrhea. The administration of psychotherapy was facilitated. The four women who became pregnant were highly pleased with the result.

### Results With Other Methods

Four patients of eighteen treated with pregnenolone alone bled more regularly. Twenty of twenty-one patients given hexestrol and pregnenolone had withdrawal bleeding. The amount of flow was slightly greater in some women after pregnenolone was added. Six of seven patients who were able to take stilbestrol 5 mg. daily for twenty days had uterine bleeding.

### Toxicity

Three patients, or 10 per cent of those treated, developed nausea of a mild nature. One of these women complained of dizziness. No other bad effects were observed. This record was very good compared to nine patients given 5 mg. of stilbestrol daily. Treatment had to be discontinued in six of them, or 66 per cent, because of nausea. However, even though nauseated, four of the six took the tablets for the first twenty-day course. Nausea also developed in a high percentage of nonpregnant women who were taking 5 mg. of stilbestrol daily for various conditions other than amenorrhea.

### Discussion

Hexestrol was found to be satisfactory for the production of estrogen withdrawal bleeding. Its use was preferred to that of stilbestrol because it could usually be given without nausea.

It was possible to predict the approximate date of the onset of bleeding and to cause a cyclic flow about once a month. The amount of blood was less than that of a normal menstruation, but the addition of pregnenolone caused a slight increase in this respect.

The cost of producing uterine bleeding was small when hexestrol was used, and it was much greater when the necessary amounts of the natural estrogens were given. However, some of the natural estrogens had an advantage in an occasional case in that they could be given without the production of nausea.

Symptomatic and psychic improvement was gratifying and, although the patients were told that the benefit was likely to be temporary, this seemed to make little difference. They regained confidence knowing that a treatment was available. The psychological advantages should not be minimized or overlooked. An opportunity would have been missed if available time during the treatment period was not used to convince the patient that she would remain in good health, even though menstruation did not occur in the months following treatment.

Of eight women who were trying to become pregnant, four succeeded. Although this therapy is not recommended for the routine treatment of sterility, it might be tried with benefit after conventional methods have failed.

There was development of the uterus in some of the patients in whom this organ was small and when menstruation occurred spontaneously in the following months, improvement seemed to be permanent.

earlier, the tablets were taken for a day or two longer and vice versa. It was thus possible to create approximately a twenty-eight-day cycle. After two or three periods of artificially produced bleeding, treatment was suspended for a month to see if menstruation would occur naturally. Future therapy was usually given in groups of two courses. When pregnenolone\* was added, it was taken from the eighteenth day of the cycle until bleeding occurred. The 5 mg. size tablets were used in a total daily dose of 5 mg. to 15 mg.

The stilbestrol was given in 5 mg. doses daily for twenty days. When pregnenolone was administered alone, the tablets were given until bleeding occurred or for one month. If menstruation started, the pregnenolone treatment was discontinued for eighteen days and then resumed.

### Clinical Material

There were three cases of primary amenorrhea, fifteen cases of secondary amenorrhea with no bleeding in six months or longer, and ten cases in which the patient menstruated less than six months previously. A physical examination was made, but no evidence of tumor or disease was found. There were thirteen single girls and fifteen married women. Two of the latter had had bilateral oophorectomies. The condition was considered to be functional in the others. Fourteen of the patients had had vaginal smear tests, and all of the slides showed a lack of cornification and a low glycogen content in the cells, indicative of estrogen deficiency. The urinary gonadotropins ranged from 6 M.U. to 42 M.U. per 24 hours in the nine patients tested, consistent with estrogen deficiency. The urinary estrogens were as low as 3 M.U. and as high as 39 M.U., averaging 18 M.U. per 24 hours in seven women. Sterility was a problem in eight women who wanted to become pregnant.

### Results With Hexestrol

Twenty-five patients, or 89 per cent of those treated, bled after hexestrol withdrawal. In three of these patients bleeding started after the second course of therapy but not after the first. Three patients did not bleed, but they had been given only one course of treatment. Two of these bled following twenty days' administration of stilbestrol, 5 mg. daily, and the third had a light flow after adding pregnenolone to the hexestrol in the second course of treatment. Twenty patients bled lightly and five moderately. The flow began on an average of four days after withdrawal of the estrogen and lasted an average of four days. There was no complaint of pain during the bleeding. Only seven women had a spontaneous menstrual period about a month following the withdrawal bleeding. Four patients previously considered to be sterile became pregnant immediately after treatment or a short time later.

There were several other physical changes due to hexestrol administration. Vaginal-cell cornification improved, and the vaginal moisture increased because of greater mucus secretion from the glands. Some improvement occurred in the uterus and accessory genitals when these parts were underdeveloped. There was greater fullness and increased sensitivity in the breasts.

All symptoms of estrogen deficiency such as nervousness, mental depression, dizziness, headaches, palpitation, hot flushes, etc., stopped during hexestrol medication.

\*The pregnenolone (Pranone) was obtained from the Schering Corporation, Bloomfield, N. J.

# A VERSATILE SELF-RETAINING TRIGGER CANNULA AND TRACTION TENACULUM FOR MODERN TUBAL INSUFFLATION AND UTEROSALPINGOGRAPHY

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MODERN technique, with accurate recording devices for tubal insufflation and utero-salpingography,\* requires a uterine cannula providing not only a gas-tight seal of the cervix for a leakproof connection between the apparatus and the pelvic cavity, but versatility to meet every contingency.

The trigger cannula (Fig. 1, a) is admirably adapted to cope with the many variations in size, shape, patency, anomalies, tumefaction, version, flexion (or combinations), met in private and clinic practice.

Newly effective occluding power is available, aided by the elasticity, resilience, and moulding quality of the rubber acorn obturator (J).

A normal external os is not necessary to obtain a leakproof seal. A portion of the acorn enters the cervical canal and occludes by direct pressure against the walls.† The smoothness of the procedure minimizes discomfort and trauma. Little time is required. The position of the uterus is not disturbed by cannulization.‡

The uterus is not displaced by the upward push of the cannula, or the downward pull of the tenaculum, because the "pull" and "push" are synchronized by the new trigger-squeezing maneuver which balances the two opposing forces, and applies them simultaneously with one hand. There is no longer any need for the operator to struggle with the cannula and tenaculum, to engage and hold them in a self-retaining manner.

The cannula gives peak performance when used with the new stainless steel traction tenaculum (D).§ However, it is able to accommodate any tenaculum or vulsellum made, from the longest to the shortest, regardless of the shape or type. It does this readily at any point of the cervix with complete ease.

The stainless steel tenaculum has new features. The design of its angular jaw, and its two finely tapered  $\frac{1}{4}$  inch teeth (O), which engage the cervix at a lower level than the shaft, but at right angles to it, give it the efficiency as a traction device which earned it its name.|| Its design, including the gracefully curved shaft, gives greatly improved access to the cervical canal without distortion. Surprisingly little trauma or bleeding results from application or removal.¶

The 8½-inch length is an advantage over shorter or longer instruments, and permits the removal of a plastic bivalve speculum of the Graves type (R), and its reinsertion, without disturbing either the cannula or tenaculum. This speculum# is also transparent to x-ray, of utmost convenience in uterosalpingography.

\*Testing of the cannula was done with the Kidde Tubal Insufflator, manufactured by the Kidde Manufacturing Co., Bloomfield, N. J.

†A larger acorn is used for the oversized patulous cervix. Acorns are readily interchanged.

‡Cannulization, a new term denoting the insertion of a uterine cannula with obturation of the cervix in a self-retaining manner.

§The cannula and tenaculum presented here are made and distributed by Clay-Adams Co., 141 East 25 St., New York, N. Y.

||A tenaculum is ordinarily a device to hold with but not for pulling or traction.

¶Removed by deliberate opening and withdrawal.

#NEICO plastic bivalve speculum, manufactured by the National Electric Instrument Manufacturing Co., Elmhurst, L.I., N. Y.

Theoretically, patients with primary ovarian failure and a normal pituitary have an excessive secretion of pituitary gonadotropin. The ovary is under continuous stimulation. The physiologic, monthly, cyclic formation of gonadotropin no longer exists. However, the administration of hexestrol in large doses for twenty of each twenty-eight days inhibits function of the ovary and pituitary and stops gonadotropin production. During the eight days when no medication is being given, the ovary is again stimulated by the pituitary, possibly improving ovarian function in some women.

### Summary

It was possible to produce withdrawal bleeding from the uterus at regular predictable intervals by the administration of hexestrol. This method of treatment was found to be safe and economical. There was a low incidence of nausea. Physical and physiological advantages were largely temporary but of definite aid for specific purposes. Psychological benefit was frequently obtained.

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Conversely, the seal is quickly tightened by "taking up the slack" with the trigger technique. Occasionally, during an uneventful procedure at higher pressures, a slight leak is noted. This is also readily dealt with.<sup>5</sup> The question arises as to whether the tone and bore of the cervix change due to the counter pressure of all obturators. The tenaculum technique provides a means of coping with this phenomenon when it occurs.

The tenaculum control screw is new in design. It is hollowed out for lightness and rapid cooling after sterilization. Its generous proportions provide excellent control and provide a plumb-bob action, returning the tenaculum control wing to the upright position automatically. A half turn holds it in any position it is turned to without further adjustment. A full turn secures it. The stainless steel shaft is very hard, and is not cut or nicked by the set screw.

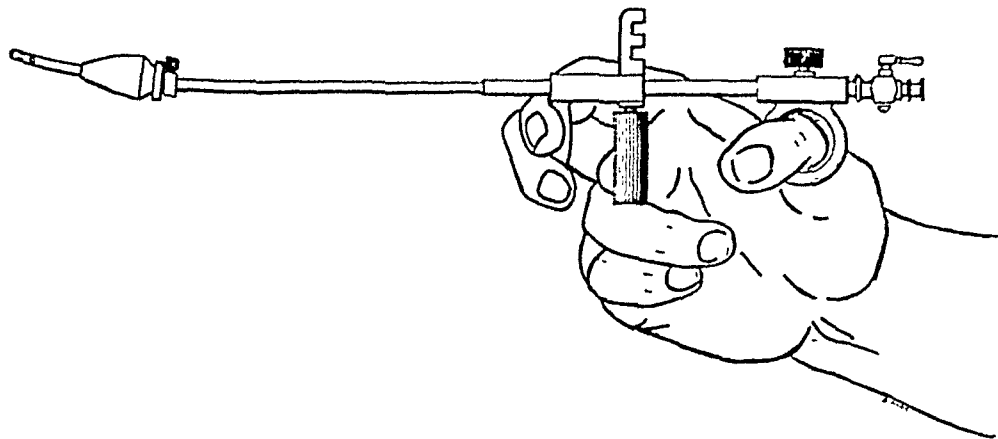


Fig. 2.—The proper way of holding the cannula for insertion into the uterus. The thumb is through the thumb ring and the fore and middle fingers are about the trigger set on the shaft.

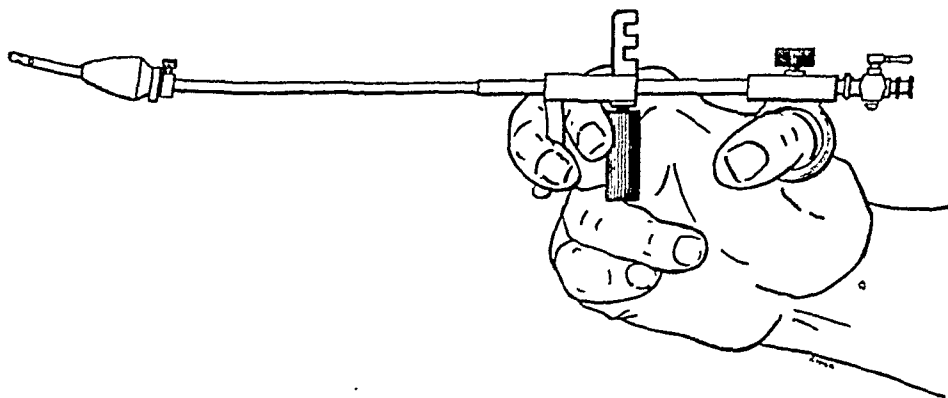


Fig. 3.—The way the tenaculum control is moved up and down the shaft to engage the tenaculum. The middle finger remains around the trigger while the forefinger is placed behind it. The tenaculum control set screw is loose.

The thumb ring, also, has a plumb-bob action when its set screw (f) is released. The thumb-ring cannula control is turned to wherever the trigger is. This, in turn, is determined by the position of the tenaculum on the cervix. The two controls act well together regardless of their position on the circumference of the control shaft.

The cannula control ring (b), when turned to the horizontal position, serves the original purpose of the cannula rings, two in number, namely, to hold the cannula when using a syringe.<sup>1</sup> It also provides for a shorter finger span to the trigger, and, when pre-set approximately where the tenaculum control will come when the tenaculum is fully engaged, acts as an auxiliary stop to prevent a possible "harpooning" action by the cannula, while it is

The speculum may be closed as pictures are taken, or withdrawn if technique calls for turning the patient.

The length of the cannula tip (K) is readily adjusted. The position of the acorn is maintained by the acorn collar screw (I). The tip is very malleable and may be rotated by turning the cannula shaft. Adjustments are, thereby, readily made for unusual depth, flexion, version, or any other distortion due to stenosis, spasm, or tumor. Occasionally, a fine two-blade uterine dilator is used before the cannula is introduced. The cannula tip has the narrowest practical diameter and is highly polished. Its end is open with four other openings near it. The tip may be passed to any point in the uterine canal.

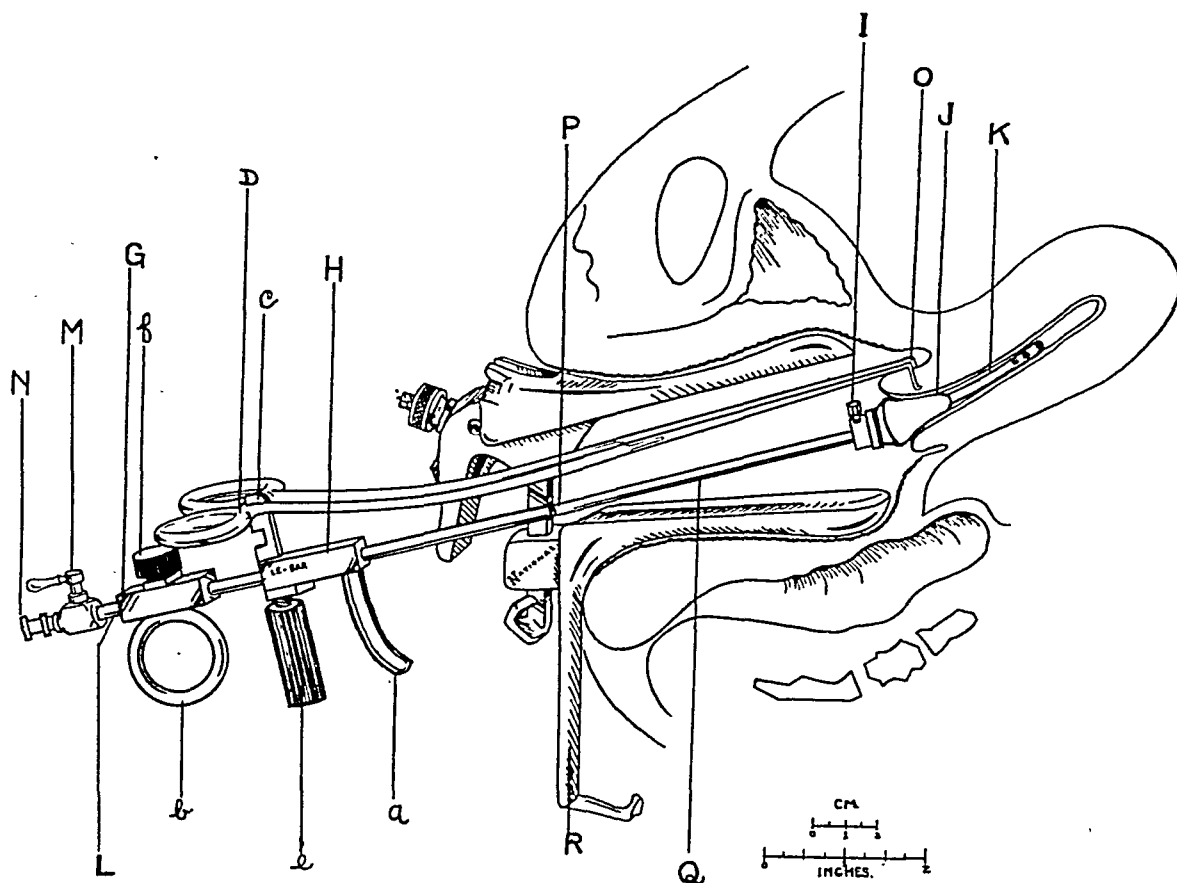


Fig 1.—Diagram showing the trigger cannula and traction tenaculum obturating the cervix with a standard rubber acorn. The tip of the uterine shaft is in the uterine canal.

H, tenaculum control: a, trigger, c, wing, e, set screw; G, cannula control: b, thumb ring, f, set screw; L, stainless steel control shaft; q, uterine shaft; P, junction of L and Q; K, malleable rotatable tip of uterine shaft; M, valve; N, luer connection; J, rubber acorn obturator; I, acorn collar and set screw; D, tenaculum cross bar; O, tenaculum jaw; R, speculum.

Provision is made for the development of deftness in inserting the cannula, and manipulating the controls. After insertion, the forefinger is placed behind the trigger to allow movement up and down the shaft (Fig. 3), with control screw open; after tenaculum is engaged, trigger is squeezed by both fingers again (Fig. 2).

A fine sense of balance is obtained by holding the instrument with thumb through thumb ring (b), and the fore and middle fingers about the trigger (a), set at the middle of the stainless steel control shaft (L). Because of this feature the cannula is a good uterine sound.

A safety feature is provided by the tenaculum control screw (e). A slight turn is all that is necessary instantaneously to break the cervical seal, with release of gas or oil pressure, if the slightest distress is shown by the patient.



### Addendum

For special work, the trigger cannula is now available with interchangeable uterine shafts at junction (P) of control shaft (L) and uterine shaft (Q). The uterine shaft connects at (P) by a Luer connection. Thus, narrower bore is available when indicated, as in the occasional severe cervical stenosis, or for use with an inflatable obturator. The trigger technique and traction tenaculum are used as with the acorn obturator for introduction and to apply sufficient traction on the cervix to prevent the inflated obturator from ballooning out of the cervix, especially when it is slightly patulous.

The use of special obturators, acorn and inflatable, and uterine shafts (tips) including biopsy curettes, with the trigger cannula and traction tenaculum, will be the basis of a future publication.

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being "pushed," should it slip through the rubber acorn. This is a possibility if the acorn collar is not tightened. The acorn screw has a heavy thread and will not fall out.

The tenaculum control wing is nonobtrusive, and performs without obstructing the view of the cervix. It does not interfere with turning the patient. It engages either the cross bar (D) or the ring front of the tenaculum. The upper notch is more convenient when engaging a large cervix, the lower one for smaller cervixes.

The cannula is of standard length, light in weight, compact, heavily chrome-plated, and functional in every way. All parts are durable for long years of hard use. The cannula is easily cleaned. It is sterilized by boiling or autoclaving. It fits readily into the average sterilizer.

An adapter, to connect an oil reservoir or syringe vertically, is available. It connects to the Luer end (N),

The cannula has a shut off valve (M) of utmost convenience during uterosalpingography.

A new cannula stand has been designed to support the cannula between the legs as the patient lies on the x-ray table.

It adjusts to a maximum height of 8 inches. It supports the cannula to prevent drag on the cervix, and permits security for the attachment of an oil reservoir or a syringe. It attaches to the stainless steel shaft in front of the valve (L). It is light, compact, and easily dismantled.

A clip-on light attaches to provide focused light on the cervix.

### Summary

A new, versatile, self-retaining trigger cannula, adapted for use with modern insufflators, is described, which will readily engage any length, shape, or type of tenaculum at any point on the cervix, by a new trigger-squeezing action which combines "pull" on the tenaculum and "push" on the cannula into a synchronized, balanced maneuver with one hand, and does not alter the anatomical position of the uterus, yet provides newly effective, nontraumatizing cervical obturation with a soft rubber acorn.

Other features include a very malleable tip, adjustable as to length, which may also be rotated.

Deftness in introducing the cannula is soon acquired because of the trigger grip and multipurpose thumb ring.

The plumb-bob action of the controls is pointed out, as is the safety feature of the tenaculum control screw which quickly releases gas or oil pressure from the cervix by a half turn.

A cannula stand to support the cannula during uterosalpingography, and to provide light to the cervix is described.

A right-angled adapter to hold a syringe vertically is described.

A traction tenaculum is discussed, including its design for pull on the cervix, greater access to the cervical canal, and the way it permits removal and reinsertion of a plastic x-ray-transparent bivalve speculum with open side.

The advantages of the tenaculum method are pointed out.

Reference is made to changes in the tone and bore of the cervix during cannulization, and how leaks thus arising are readily controlled by the tenaculum.

I wish to express grateful acknowledgment to Dr. Julius Jarcho and Dr. Peter Murray of the Department of Obstetrics and Gynecology of Sydenham Hospital for their kind cooperation in the experimental phases of the trigger cannula and traction tenaculum.

I also express my gratitude to Dr. George Berson and Dr. Leon Zussman of the Department of Obstetrics and Gynecology of Sydenham Hospital.

I also wish to express my thanks to Faith Hope Kahn, R.N., for her assistance during the research and clinical testing of the instrument and also her patience in the preparation of this manuscript.

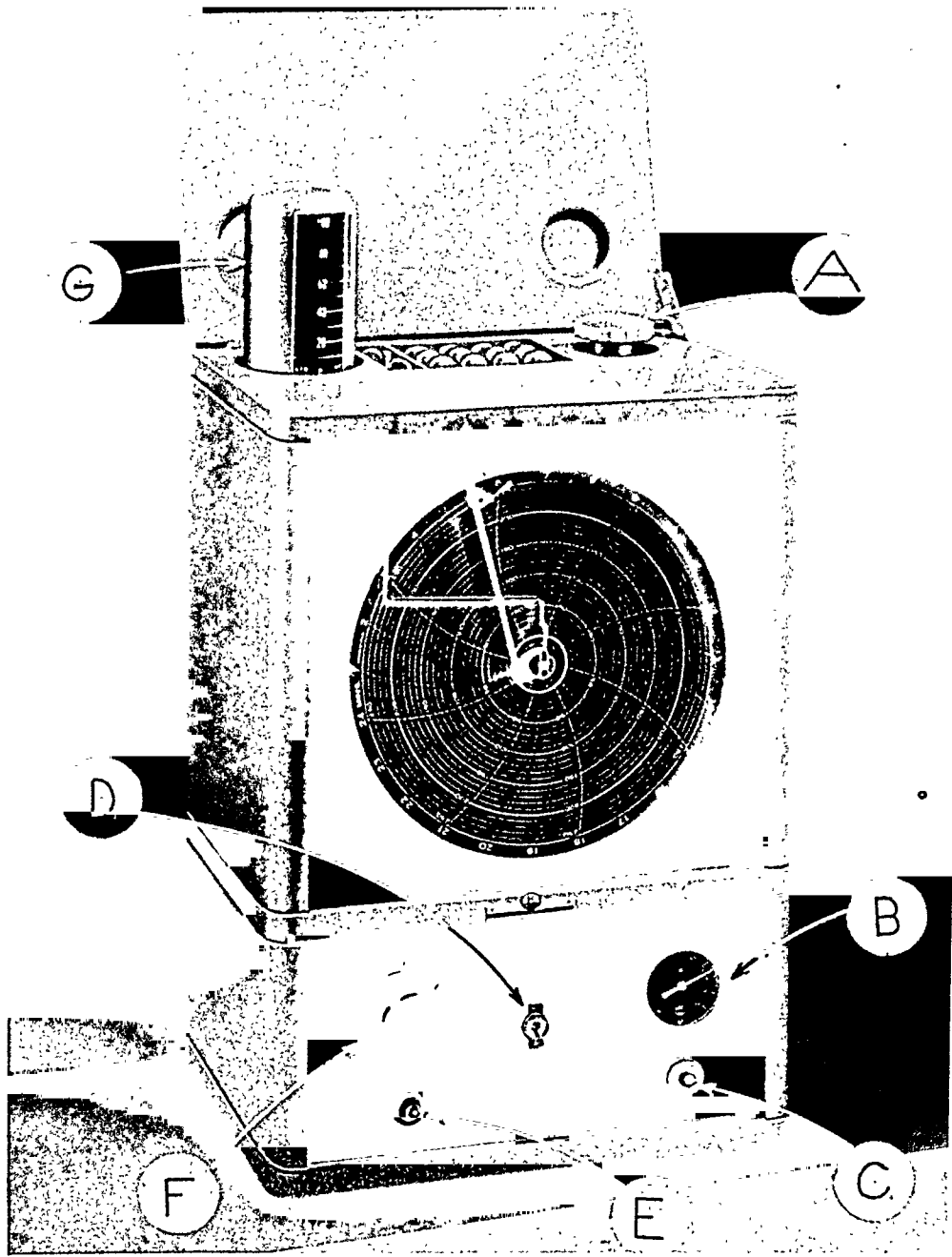


Fig. 1.—Tubal insufflator.

## NEW TUBAL INSUFFLATOR WITH AUTOMATIC VOLUME AND PRESSURE CONTROL

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*(From the Department of Obstetrics and Gynecology, Cornell University Medical College and the New York Hospital)*

UP TO 1946, the tubal insufflation apparatus in current use required skilled manipulation and constant attention. Carelessness in its use could end in unhappy results.

A few years ago, it occurred to one of us (I. B.) that if the apparatus were simplified and made completely automatic and thereby safe, this would popularize it among physicians and give it a wider range of usefulness in the study of the sterile couple. Accordingly, the problem was taken to Charles Davies, A.S.M.E., industrial designer, who designed and engineered the apparatus herein described. This paper deals with an apparatus which eliminates many of the drawbacks and hazards of the current insufflation machines, and which has been designed in such a fashion that accidents due to failure to take mechanical precautions are impossible.

The principle embodied in the final production model herewith illustrated is that of a constant pressure-maximum volume gasometer. By the use of this device, the total uterine pressure is automatically controlled so that at no time can it exceed a pressure of 200 mm. mercury. Moreover, at no time during a test can more than 100 c.c. of carbon dioxide be injected into the uterus.

The machine has been designed for utmost simplicity. On the front panel are two dials. The large central one is the electrically operated kymograph with a special chart designed for clear visibility. The lower right hand dial B indicates the volume of gas in the storage chamber. Beneath this dial is a push button C, which charges the gasometer. In the center of the lower panel is the electric switch D, which operates the kymograph. On the left-hand side is a knob F, marked 0, 30, and 60, which controls the speed per minute in cubic centimeters of the gas flow. Beneath this knob is the outlet E, into which the cannula is plugged.

The push button C actuates a two-way bypass valve. This device contains two valves, one leading to the gasometer, the other to the cannula outlet. It operates as follows: When the button is pressed, it opens the connection between the gas storage chamber and the gasometer, and at the same time closes the connection to the cannula. Gas then fills the gasometer. When the button is released, it closes the connection between the gas storage chamber and the gasometer and opens the one leading from the gasometer to the cannula. Thus, it is possible to recharge the gasometer, if it becomes necessary, without removing the cannula from the cervix.

The rate of gas flow through the cannula is controlled by a needle valve, which is operated by the knob F. This can be set at any speed up to 60 c.c. per minute.

The whole machine is enclosed in a sturdy portable aluminum cabinet and weighs twenty-five pounds. Provision is made to store one dozen cartridges, the cannula and the writing ink under the lid of the cabinet.

*Operation of the Apparatus.*—To charge the apparatus, a carbon dioxide cartridge is screwed into the opening at A. The needle on the lower right hand dial B, which indicates the quantity of gas in the storage chamber, will swing over to "full." By pushing the button C, gas enters the gasometer and forces the piston G to rise. This piston is calibrated so that when it reaches the mark, zero, the gasometer contains 100 c.c. at a pressure of 200

## SUGGESTION FOR IMPROVEMENT OF STIRRUP ATTACHMENT FOR OPERATING TABLES

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*(From the Vincent Memorial Hospital, the Gynecologic Service of the Massachusetts General Hospital)*

**D**URING the past year a modification of the usual operating table stirrup attachments for supporting the legs of a patient in lithotomy position has been in use at the Massachusetts General Hospital. Modification of the leg holders which have been standard equipment on operating tables for many years was suggested by the frequent occurrence of calf tenderness and pain following their use. As illustrated below (Fig. 1) the passage of the legs lateral to the vertical supporting rods subjects the calves to considerable pressure. This is not infrequently increased by assistants leaning against the legs. In addition to the discomfort caused the patient it is impossible to distinguish these signs and symptoms from those of early phlebothrombosis and thrombophlebitis originating in the calves. Indeed, pressure and contusion of the calves produced by the old leg holders have frequently been suspected as etiological factors.

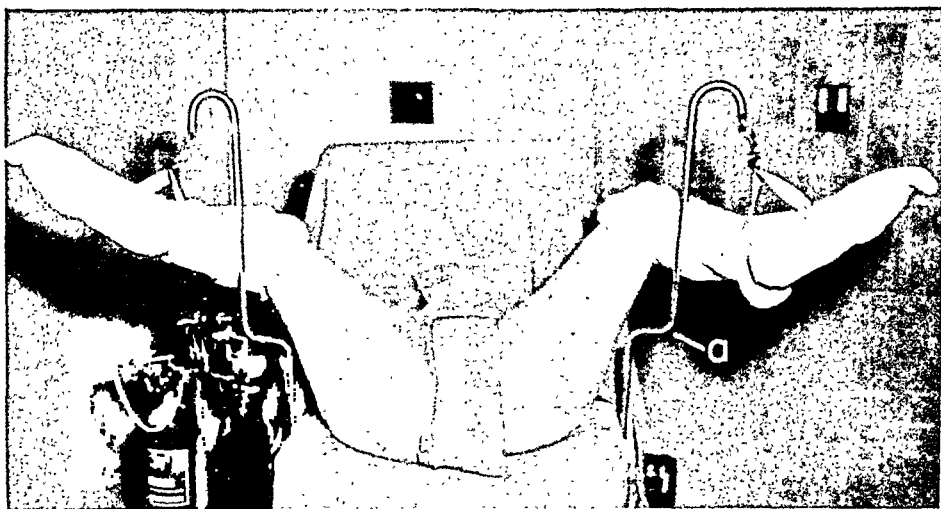


Fig. 1.—The old type leg holders and their method of use. The pressure on the calves is shown. The abduction of the thighs necessary for passage of the legs lateral to the vertical bars subjects the abductor muscles to considerable strain and the tension upon these muscles can be seen.

These considerations have led to the abandonment of mechanical leg holders in some clinics or the substitution of other types of holders which have similar objectionable features or have not given satisfactory exposure of the perineal region.

The shape and method of use of the old and modified stirrups are shown in Figs. 1 and 2. The alterations consist in cutting the bar at "a", reversing the direction of the vertical rod and hook, inserting a 7-inch horizontal extension, and welding the pieces together.

mm. mercury. Even if the push button is held down after the piston has attained its maximum point, the pressure and volume will not exceed the limits established because of the mediation of a safety valve which allows excess gas to escape.

The apparatus is now ready for operation. The patency of the cannula is tested by turning the knob F to the mark 60, and watching the kymograph needle. If the pressure rises, the cannula is plugged; if it remains at zero, patency is established.

The cannula is introduced into the cervix; the knob F is turned to 60 (rate of flow); the electric switch D is turned on to start the kymograph, and the test proceeds. With a self-retaining cannula, the physician's hands and attention are completely free. Should the pressure reach 200 mm. mercury, there is assurance that it can go no higher so that all danger from this source is eliminated. If, however, the tubes are patent, there is assurance that no more than 100 c.c. of carbon dioxide can possibly be introduced.

In the event that gas has been lost through leakage at the cervix and it is desired to repeat the test, the gasometer can be recharged without removing the cannula or closing the needle valve F. The two-way bypass valve previously mentioned, which is operated by the push button C, prevents gas from flowing through the cannula while the gasometer is being charged. As soon as the button is released, gas will again flow through the cannula.

The kymograph chart is designed for visibility. It has thick rulings at 50, 100, 150, and 200 mm. pressure points, as well as radial markings which indicate three-minute periods. Once tubal patency has been demonstrated and a protracted record of tubal excursions is desired, the knob F can be turned to a point between 30 and 60 so as to slow down the speed at which carbon dioxide enters the uterus. In this way, the amount of gas introduced can be kept at a minimum, assuring the least amount of discomfort to the patient from shoulder pain.

The working model of this apparatus has been in use for over one year by the authors in private practice. A production model is now being used in the Sterility Clinic of the New York Hospital. The apparatus has proved itself to be completely reliable and simple to operate. It eliminates the confusion caused by the numerous controls and the vigilance required in the use of other existing types of apparatus.

(Produced by the Kidde Manufacturing Company, Bloomfield, New Jersey.)

# Department of Reviews and Abstracts

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## Selected Abstracts

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### Gynecology

Bassan, D., and Borches, F.: Acute Ulcers of the Vulva, *Bol. Soc. de obst. y ginec. de Buenos Aires* 26: 68-73, Sept. 12, 1946.

The author, after reviewing Hunt's and Lipschutz's classifications of vulval ulceration, describes a case of acute vulval ulcer in a woman 47 years of age. While she was relieved rapidly with topical sulfonamide powder and 400,000 Oxford Units of penicillin, the author stresses the importance of vitamin B complex deficiencies in these cases, noting particularly moderate ariboflavinosis.

CLAIR E. FOLSOME.

Borjas, A., and Rodriguez-Diaz, L. H.: Vesicovaginal Fistula of Tubercular Origin, *Rev. obst. y ginec.* 7: 215-221, 1947.

The authors describe in detail a case of urinary tuberculosis in a girl of 14 years which resulted in the development of an incurable vesicovaginal fistula. Treatment consisted of left nephrectomy and a right ureterocolostomy.

CLAIR E. FOLSOME.

Bettinger, H. F., and Jacobs, Hubert: Mesonephroma Ovarii, *M. J. Australia* 1: 100, Jan. 24, 1948.

The authors report a case of this "rare" type of ovarian tumor and review the clinical and pathological findings. The tumor has no endocrine secretions and does not therefore cause any general symptoms that might lead to a specific diagnosis. It is felt that these tumors as a whole should be considered as malignant. A discussion of Schiller's contentions as to the histogenesis of these tumors is presented. The authors urge close observation for further cases of this type of tumor in order to scrutinize a more composite group of such tumors.

WM. BERMAN.

Fluhmann, C. F.: The Clinical Significance of Chronic Parametritis, *California & West. Med.* 68: 159, March, 1948.

It has long been recognized that the parametrium plays an important role in serious and extensive diseases of the uterus such as inflammations, carcinoma, and endometriosis. However, the purpose of this report is a study of 54 patients observed in private practice, in whom a variation of symptoms, from vague lower abdominal pain, backache, and leg pains, had been attributed to demonstrable thickening of the sacrouterine ligaments.

A positive diagnosis is based on two procedures which put the cervix on a stretch and thus the inflamed uterosacral ligaments can be definitely felt as tender cords.

The treatment consists essentially of two procedures: In the first place, elimination of any inflammatory lesion of the cervix with or without erosion of that organ; second, the application of heat, which may be accomplished by diathermy or hot Sitz baths with continuous douche. This should be done for twenty minutes once or twice daily.

This allows the vertical bar to pass lateral to the legs and still support the legs from the same position as previously. There is no appreciable torque tending to rotate the vertical support since the weight of the legs is supported in a vertical direction and the horizontal thrust falls in the plane of the attachment to the table.



Fig. 2.—The modified leg holders and their method of use. The calves do not touch the supports. The thighs are somewhat more flexed but not abducted unnecessarily. Exposure of the perineal region is fully as adequate as with the other type of holders.

Exposure of the perineal region is entirely satisfactory. The thighs are somewhat more flexed and marked abduction necessary for passage of the legs lateral to the vertical rods of the old stirrups is avoided. Assistants stand in the same position as previously, either inside or opposite the patient's feet.

Any machine shop can alter the old stirrups or construct new ones at slight cost.

Mr. George T. Frawley of the Machine Shop of the Massachusetts General Hospital kindly fashioned the new leg holder from an old one.



San Martin, H. G.: *An Illustration of Conservative Gynecologic Surgery*, *Obst. y ginec. latino-am.* 5: 496-500, Oct., 1947.

The author, Professor of Clinical Obstetrics at Uruguay National Medical School, Montevideo, emphasizes his plea for conservative gynecological surgery by presentation of a unique case report. A 20-year-old primiparous patient, after several outside attempts to produce an abortion, from a three months' pregnancy, with some caustic intrauterine substance, was operated upon from above and a partial hysterectomy was performed. The fetus was dead. Four months later the patient became pregnant again, despite advice to the contrary, and was delivered ultimately of a living child weighing 4,100 Gm. Her recovery was full and complete.

CLAIR E. FOLSOME.

### Labor, Management, Complications

Perez, Luis, and Blanchard, Oscar: *Prophylactic Local Chemotherapy in Operative Obstetrics*, *Anales del Instituto de Maternidad y Asistencia Social*, "Professor U. Fernandez" 7: 9-26, 1945.

The authors reporting from the de Alvear Hospital of Buenos Aires, review their experiences following the use of 5.0 Gm. of sulfonamides which had been placed in the uterine cavity following operative childbirth; e.g., forceps, and removal of the placenta. The authors have developed an intrauterine instillator, capable of being sterilized, which aids in placement of the sulfonamide powder. In an earlier report they obtained only 5.0 per cent morbidity among a series of 80 cases. To this number 65 more cases are added for a total of 145 cases. They have used the intrauterine application of sulfonamides in more serious indications in the latter series. They obtained an over-all morbidity of 11.8 per cent, most of which were of a mild or transient character.

They conclude that the intrauterine application of sulfonamide powders represents an advance in prognostic progress since the patients obtain prophylaxis against septic complications in operative obstetric deliveries.

CLAIR E. FOLSOME.

Gillman, J., Gilbert, C., and Gillman, T.: *Puerperal Inversion of the Uterus of Nutritional Origin—An Experimental Study in the Albino Rat*, *South African J. M. Sc.* 12: 161, Dec., 1947.

Five of twenty parturient rats, raised on corn and soybean meal, underwent a spontaneous uterine inversion. These animals were malnourished and stunted, and mild rachitic changes were present in two cases. These observations indicate that mismanagement of the third stage of labor is not the only cause for inversion, but that a metabolic defect may predispose by an impairment of uterine contraction mechanisms.

IRVING L. FRANK.

### Menopause

Kernodle, John R., and Cuyler, W. Kenneth: *Vaginal Cytology of Postmenopausal Women*, *South. M. J.* 41: 861, Oct., 1948.

Using the technique of Papanicolaou and Traut, the authors have studied and classified the postmenopausal vaginal cytology. They divide the nonmalignant epithelial cells into five types: follicular, regressive, premenstrual, crowded menopause, and atrophic menopause. For still greater definition they employ four additional subtypes which in their opinion clarify the description of cellular morphology. From the study it is felt that the subtypes may represent physiologic, morphologic changes in the vaginal epithelium from the menopause to senility.

The results are tabulated. It is noted that, of the 33 patients, 14 were completely free of symptoms and in them no evidence of thickened sacrouterine ligaments could be palpated. Definite improvement occurred in thirteen instances; in six cases there was no relief. However, of those cured or improved, six later returned with recurrence both of symptoms and the physical findings.

JAMES P. MARR.

**Bayan, Flora B.: Increased Incidence of Prolapse of the Uterus as Probable Effect of War, Philippine J. Surg. 2: 201, Sept.-Oct., 1947.**

The author reports 32 cases of uterine prolapse admitted to the Philippine General Hospital in nine months, a tenfold increase in incidence as compared with prewar years. This increase is attributed to heavy physical burdens placed on women during the war, and to near-starvation. In 12.5 per cent of these women there were definite manifestations of malnutrition.

IRVING L. FRANK.

### Gynecologic Operations

**Jacobson, Philip: Preservation of Function in Cystic and Sclerotic Ovaries, Surg., Gynec. & Obst., page 31, July, 1948.**

The author presents sixteen patients from whom both tubes and one ovary had previously been removed. These patients were suffering from ovarian insufficiency of the one remaining ovary. Exploration revealed that these ovaries contained numerous small "morbid follicles" which were located just between the white lines and impinged on the vessels and nerves as they entered the ovary. Removal of these follicles with preservation of the ovary brought relief from discomfort and restoration of normal cyclic activity at least temporarily to the patients so treated. The author presents in detail the technique of exploring the hilum of the ovary. A plea is made for more conservative surgery in dealing with this type of case.

L. M. HELLMAN.

**D'Ingianni, Vincente: Reconstructive Surgery of the Fallopian Tubes Employing a Canula, South. M. J. 41: 575, July, 1948.**

Surgical reconstruction of occluded Fallopian tubes has been in the past a most unsatisfactory procedure. A review of 818 plastic operations on the tubes resulted in only 36 live-born babies. The new technique here described gave a 20 per cent live birth incidence, as compared with the 6.6 per cent in the large series of 818 operations performed by various techniques and many operators. The technique of this new operation is well illustrated. The tube is divided distal to the occluded portion and a steel cannula 3 cm. long is passed into the liberated, patent lumen. To this cannula there is welded a long flexible wire. An incision is made in the fundus and the tube and its included cannula are passed into the uterine cavity, the wire being forced down through the cervical canal to permit removal of the cannula three months after operation. The serosa of the tube is sutured to the serosa of the uterine fundus. When occlusion at the fimbria is found, the distal portion of the tube must be resected and the serosa and mucosa approximated before transplantation of the proximal cut end of the tube.

WILLIAM BICKERS.

**Bianco, Alfonso A.: Giant Myxoma of the Vulva, An. brasil. de gynec. 24: 345-350, Nov., 1947.**

Bianco describes an unusual vulval tumor removed from a 20-year-old patient. The tumor began as a small lesion upon the right labium majus. In four months it had grown so rapidly the patient was unable to walk. The mass was removed under local anesthesia. It weighed 6 kg. (13¼ pounds) and measured 42.0 by 29.0 cm. (about 17 by 11 inches). It was multilobulated with 9 major lobules. Microscopic study revealed it to be a myxoma. Three photographs and a good bibliography of these rare lesions are included in the article.

CLAIR E. FOLSOME.

Urine collected from the cloaca of the toad is examined every thirty minutes over a three-hour period. If the test is positive, numerous and characteristic spermatozoa are found in the cloacal fluid. None are found in a negative test. These toads were found to liberate free sperm consistently into the cloacal fluid when injected with 20 U. of chorionic gonadotropin. Spermatozoa could not be obtained following injections of estrone, progesterone, water, or saline. Increasing the concentration of gonadotropin does not hasten the response to the test. Normally, sperm are found in the cloacal fluid of these gray toads only at time of their sexual embraces.

The authors studied fifty clinical human cases where the amenorrheic period exceeded the usual time of the cycle in a range of 5 to 50 days. They found positive results varied in appearing positive in a time range of 30 to 120 minutes. The results checked in a control series of Friedman tests. They utilized the new test to pick up and operate on two ectopic pregnancies. They conclude the test is valuable, much more rapid, and as reliable as the Friedman test. Five photographs are included.

CLAIR E. FOLSOME.

### Placenta

Baens, A., and Tancinco-Yambao, G.: Report on 80 Cases of Ablatio Placentae, Philippine J. Surg., March, April, 1948.

In a twelve-year period there were eight cases of ablatio placentae at the Philippine General Hospital, an incidence of 1:985. The apparent etiologic factors were: toxemias, 21; trauma, 3; pulmonary tuberculosis, 3; appendicitis, 1; acute ileocolitis, 1; and rectal carcinoma, 1. In fifty patients the cause was undetermined. In two-thirds of cases there was abdominal pain and a ligneous uterus, while the remainder had a lax nontender uterus. Ninety-four per cent of patients had slight to moderate vaginal bleeding. Forty-nine of the patients were delivered vaginally, twenty-four spontaneously.

The gross maternal mortality was nineteen, or 23.75 per cent. Seven deaths were due to peritonitis following cesarean section (including three cesarean-hysterectomies). There were nine hemorrhage-shock deaths, five following cesareans (including two cesarean-hysterectomies), three following vaginal delivery, and one undelivered. Two patients delivered extramurally died of postpartum hemorrhage, and one patient died of uremia. The mortality rate in the group delivered by cesarean section was 40 per cent (usually more seriously ill patients), and in the group delivered vaginally was 6 per cent.

IRVING L. FRANK.

### Physiology of Pregnancy

Davis, Edward M., and Seski, Arthur: Childbearing in the Twilight Reproductive Period, Surg., Gynec. & Obst., page 145, August, 1948.

A study is made of the obstetrical histories of 11,011 women, 40 years old and older, who were cared for in The Chicago Lying-in Hospital during the years 1927 through 1944. This study confirms the findings of numerous articles on this subject. The infant mortality of this group of women is definitely higher than the hospital rate over the same period, being 9.5 per cent and 3.5 per cent, respectively. There is approximately a three-fold increase in the incidence of hypertensive complications of pregnancy. Placenta previa and premature separation of the placenta were increased materially. Labor was marked by an increase in operative intervention as a result of pregnancy complications. The authors conclude that there are many real hazards associated with pregnancy in older women.

L. M. HELLMAN.

Smears suspicious of carcinoma, but not definitely diagnostic were seen most frequently in the regressive type of smear. And the same type was most frequently associated with proved malignancy. Three known malignancies were not diagnosed by either vaginal or cervical smears, an error of 4.2 per cent. There were 70 cases of proved malignancy and, of these, 12.9 per cent were diagnosed only by cervical smear.

WILLIAM BICKERS.

Ferguson, Homer E.: The Use of Vitamin E in Menopausal Syndrome, Virginia M. Monthly, page 447, Sept., 1948.

Indiscriminate use of the estrogens in the treatment of the menopause is fraught with great danger to the patient if used by inexperienced physicians. Sedation and verbal assurance have an important place in the treatment, but the patient demands more. The author seems to think that vitamin E has proved of unquestionable value in certain reproductive disorders of male and female; namely, threatened and habitual abortion and also in certain neuromuscular diseases such as disseminated sclerosis. There are many who disagree. Vitamin E was first used in the menopausal syndrome by Christy and subsequently confirmed by Hain. The author reports experience with some 66 cases using 10 mg. of alpha-tocopherol three times daily for 6 weeks and then 5 mg. daily for indefinite periods. A fair number of these patients received complete relief or significant reduction of symptoms referable to vasomotor instability.

WILLIAM BICKERS.

### Miscellaneous

Chesley, Ray F.: Progress Report on Observations of the In Vitro Effect on Antibiotics, Sulfonamide Drugs and Combinations Thereof Upon Several Strains of Pathogenic Bacteria, Bull. Margaret Hague Maternity Hosp., page 59, June, 1948.

The author concludes from in vitro experiments with various chemotherapeutic and antibiotic substances that a combination of penicillin with sulfathiazole is most efficient because it has the widest bacteriocidal range with the lowest cost. He warns against prophylactic use of these agents in dosage or duration that fall short of the full therapeutic range because of the development of increased bacterial resistance. This report emphasizes that these results might differ in vivo, and, therefore, concludes that clinical evaluation would be necessary to supplement these studies.

S. B. GUSBERG.

Croxatto, H., Croxatto, R., and Reyes, M.: The Effect of Hypertension on the Inactivation of Oxytocin by the Serum of Pregnant Women, Science 108: 658, Dec., 1948.

In a small series of experiments the authors have shown that the enzyme oxytocinase which ordinarily reacts on the substrate oxytocin to reduce its activity will also exert an inhibitory effect on added hypertensin. The latter slowly disappears as the incubation process progresses and hypertensin is destroyed. Parallel experiments were performed showing that hypertensin also inhibits the inactivation of vasopressin. All of these experiments were performed using rat and guinea pig uteri to measure the oxytocinase activity of the blood plasma. They indicate an extremely close relationship between the enzymatic systems that inactivate hypertensin, oxytocin, and vasopressin. The possibility that these cross effects operate also in vivo is now under investigation.

L. M. HELLMAN.

Lima, Octavio Rodrigues, and Pereira, Oswaldo Gelli: A Biological Pregnancy Test Using the Male *Bufo Marinus*, An. brasil. de gynec. 24: 245-252, October, 1947.

The authors, reporting from the Obstetrical Clinic and Pathology Department of the University of Brazil National Medical School, evaluated a new pregnancy test using the male *Bufo marinus*. Ten c.c. of a morning urine specimen are injected into the dorsal lymph sac.

In considering the data on the nonpregnant woman one can see a striking difference in morphine action on the normal patients and on the patients with diabetes insipidus. In the normal patients there appears to have been a striking oliguria during the peak of morphine action amounting to an almost complete suppression of urine flow. In the two patients on whom detailed protocols are available, Kraushaar and associates report marked inhibition of water diuresis (5 per cent of the control excretion for E. M. and 8 per cent for E. S. for the eight-hour period). In the first group of nine normal nonpregnant women detailed data are not available, but it appears that the women eight hours after morphine excreted 48 per cent of the amount put out in the control period. It is hard to understand this startling difference in morphine action. In contrast is the finding of a relatively small decrease in the patients with diabetes insipidus (66 and 72 per cent, respectively, of the control excretions). The fact that some decrease in the diuresis occurred may be attributed to some factors altering renal dynamics or more probably to a minimal output of antidiuretic hormone from small neurohypophyseal remnants. These patients cannot be assumed to have maximal polyuria, such as occurs when there is complete absence of antidiuretic-hormone-producing tissue, merely on the basis of the saline infusion test of Hickey and Hare (incorrectly attributed to Carter and Robbins who merely confirmed the original observations).

Although Kraushaar and co-workers do not mention the severity of the diabetes insipidus in their patients, I would infer from their published charts that the patient L. B. excreted about 6 L. of urine per day and the patient M. D. between 3 and 4 L. per day. If these estimates are correct, it would seem certain that these patients were far from having the maximal polyuria which is characteristic of the individual with no antidiuretic-hormone-secreting tissue. It will be recalled that in the total absence of the antidiuretic hormone 12.5 per cent of the glomerular filtrate appears as urine. Thus, if the facultative reabsorption—normally controlled by the antidiuretic hormone—fails to occur, one-eighth of the 180 L. (130 c.c. per minute multiplied by 1,440 minutes per day), i.e., 20 L. of urine are excreted each day. In a hydrated patient with diabetes insipidus smaller output might be ascribed to low rate of glomerular filtration or to the presence of a small amount of antidiuretic hormone secreted from uninvolved neurohypophyseal tissue. In response to morphine stimulation, these remaining cells appear to put out augmented amounts of hormone. This may well be the case in the patients reported by Kraushaar and co-workers. In any case, I feel sure that the marked suppression of diuresis seen in the normal women contrasts so impressively with the slight change in these patients with only incomplete diabetes insipidus that one cannot deny the importance of the neurohypophyseal mechanism in morphine antidiuresis in human beings.

Kraushaar and associates place a great deal of weight on the failure of the patients, pregnant and nonpregnant, to show a chloruresis with morphine. In our dogs we were usually but not always able to demonstrate an increase in total chloride output after morphine. This is in good agreement with the results of the workers using physiologic doses of Pitressin (1 to 15 milliunits).<sup>2, 3</sup> Stimulation of neurohypophysis likewise produces an increase in total chloride excretion only part of the time. It seems unnecessary to place so much emphasis on so controversial a change as chloruresis especially when the findings are at best equivocal. The crucial experiment would be the study of the effect of morphine on water diuresis in patients with complete diabetes insipidus.

It seems to me that it is very difficult to draw any conclusions from the data presented by Kraushaar and co-workers. I certainly cannot see any experimental fact in their work that would contradict our concept, namely that the hypothalamico-hypophyseal system is involved in morphine antidiuresis.

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MAY 28, 1949

## Correspondence

### Comments on the Antidiuretic Action of Morphine

*To the Editor:*

In an article entitled "Morphine Suppression of Urinary Output in Pregnant and Nonpregnant Women" (AM. J. OBST. & GYN. 57: 302, 1949) Kraushaar, O. F., Bradbury, J. T., Wang, Y. K., and Brown, W. E., referring to our previous work,<sup>1</sup> have concluded: "... that the data from dog experiments, indicating that morphine causes a release of antidiuretic hormone from the neurohypophysis, cannot be accepted in explanation of the antidiuretic effect of morphine in normal women." I should like to take exception to this statement, for I feel that their conclusion is hardly justified. A critical examination of their experimental findings reveals no contradiction, but if anything rather a confirmation of our concept of a neurohypophysial mechanism for morphine antidiuresis.

This concept is based on experiments done on female dogs maintained on standard diets. When such animals in postabsorptive state and in water equilibrium are given water, either by stomach (40 c.c. per kilogram of body weight) or by intravenous infusion (25 c.c. per kilogram), they excrete it practically quantitatively within three hours. The water administered by stomach has been shown to be completely absorbed from the gastrointestinal tract in forty minutes. Morphine, when given either forty minutes after the administration of water by stomach or fifteen minutes before the intravenous infusion of water is started, inhibits water diuresis, the excreted amount falling to 13 per cent (1 to 30 per cent) of the water intake. In dogs with diabetes insipidus produced by interruption of the hypothalamico-hypophysial tract (the so-called neurohypophysectomized animals), morphine does not inhibit the diuresis produced by water given either by stomach or by vein. It has been concluded, therefore, that morphine exerts an antidiuretic effect acting on the hypothalamico-hypophysial system and thereby liberating antidiuretic hormone.

Before examining the data of Kraushaar and co-workers I should like to comment on their techniques. In order to study drug action on water diuresis one must devise a uniform method that produces a clear-cut water diuresis in every subject. In their experiments, the amount of fluid infused into their subjects was not constant, and the time of infusion varied between three and six and one-half hours, while the collection period remained constant (eight hours). During the eight-hour period before starting the infusion of 5 per cent glucose, no fluid was given so that at the start of the experiment the patients were not in water balance. Furthermore, a diuresis induced by 5 per cent glucose solution is hardly the same as that produced by water alone. It is not surprising, therefore, that only a few of their patients returned the entire water load within the eight-hour period of observation. These results clearly indicate that the method devised for inducing water diuresis was not suitable.

It is well established that pregnant women have a greatly increased volume of body water and in view of this fact and the other variables involved in water exchange they should not be compared with nonpregnant women with diabetes insipidus. This criticism is justified since the pregnant woman, M. B., showed no significant antidiuresis with 2 units of aqueous Pitressin, while the nonpregnant patient, M. S., showed a significant antidiuretic effect with 5 units of Pitressin tannate in oil. (Comparable controls would, of course, have been more informative.)

of morphine. It is also probable that adequate clinical studies will yield positive evidence to confirm his concept of the hypothalamico-hypophysial system being involved in morphine antidiuresis; our evidence, being negative, is not contradictory.

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JUNE 25, 1949

## Fetal Heart Rate and Posterior Pituitary Extracts by Intravenous Drip

*To the Editor:*

Rupture of the uterus is recognized as a rare but definite danger associated with the use of Pituitrin intramuscularly for induction of labor. With the increasingly widespread use of this agent by intravenous drip, there appears to be danger to the fetus, but it is a danger which due attention to essential precautions will prevent. In some unpredictable instances, marked and prolonged slowing of the fetal heartbeat may occur. The uterine sign for this is a sustained uterine contraction lasting many minutes and involving the entire uterus or only its upper part. Normal fetal heart rate returns at once, upon decrease in the rate of administration or complete withdrawal of Pituitrin. Relief of fetal distress is associated with prompt relaxation of the uterine contraction and establishment of rhythmic activity. Our experience is as follows:

Records of uterine contractions have been made with a two-channel, ink-writing strain-gage tokodynamometer similar in principle to the three-channel one reported by Reynolds, Heard, Bruns, and Hellman (1947). Activity is recorded from the middle portion of the upper third of the uterus (fundus) and from the middle of the lower third of the uterus (lower uterine segment.) Intravenous drip of Pituitrin (1:5,000-10,000 concentration) is begun by way of the cubital vein.

Pituitrin was administered for the purpose of inducing labor or of accelerating an otherwise prolonged first stage of labor. At the time of injection a team of two was stationed with the patient constantly, one to observe the subject, to listen to the fetal heartbeat, and to regulate most carefully the rate of the intravenous drip; the second member of the team to operate the tokodynamometer and to watch the record of the activity of the uterus.

Upon starting the intravenous drip a period of adjustment was usually required to establish a flow at the desired rate of 0.5 minim per half-hour or less. During the period of fluctuation in the rate of flow the uterus responds promptly, contracting only in the upper region. On two occasions, at the onset of the administration of Pituitrin for induction of labor, sustained contractions lasting for several minutes were observed. In one, the fetal heart rate prior to the injection was 120 per minute. During a contraction lasting seven minutes the fetal heart rate diminished to 88 per minute. In the second case, the fetal heart rate dropped from 168 per minute to 80 per minute during a contraction lasting ten minutes. Upon withdrawal of the Pituitrin the uterus promptly relaxed and the fetal heart rate returned to normal.

In view of the fact that this result was observed in two instances where Pituitrin was used in the dilutions mentioned above, we believe that a warning should be sounded with respect to this danger. Theobald and associates and Hellman and associates have noted this effect, but have not stressed it. Although the published reports on this technique are few (Hellman, 1949; Hellman, Harris and Reynolds, 1949; Stone, 1949; Theobald, Graham, Campbell, Gange, and Driscoll, 1948), reports of its use made to several societies have led to rather widespread adoption of this procedure at the present time in several metropolitan areas in this country. As a result, the technique is now becoming recognized as one of considerable potential value. It offers a means of continuous, even dosage and

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2. Shannon, J. A.: *J. Exper. Med.* 76: 387, 1942.
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## Reply by Drs. Kraushaar and Bradbury

*To the Editor:*

The impetus and the pattern for our recent observations developed largely from de Bodo's excellent studies. In our study, the dosage of morphine and the quantities of fluid administered were limited to those that are commonly employed in the clinical management of patients. Under these conditions, morphine injections were consistent in suppressing urine volume but did not produce a chloruresis. Our conclusions should be interpreted as indicating that the findings in women failed to give any positive evidence on the mechanism of action of morphine, but in no way do they detract from the validity and decisiveness of de Bodo's contributions.

De Bodo's criticism, that the amount of fluid and the duration of the infusion were not constant in our patients, is valid, but, we think, unimportant. Each woman was regarded as an experimental unit, who could be treated as a control on one day and as an experimental subject a few days later. Such a program is logical as long as the amount of fluid and the rate of injection are kept constant during the two study periods in the same patient. This provides a better comparison than using different individuals for the control and experimental tests.

We are not impressed by his suggestion that our subjects were not in water balance at the beginning of the infusion. Strictly speaking, a person would never be in water balance unless a continuous infusion were being given which would equal the urine flow plus the insensible loss. Furthermore, experiments in our laboratory have shown entirely comparable urine volumes following the administration of equal volumes of fluid, whether it be water by mouth, or 5 per cent or 25 per cent glucose solution given intravenously. (Glucose is grossly overrated as a diuretic agent.) Since these observations were preliminary to an evaluation of the therapeutic use of morphine in women with toxemia of pregnancy, we were primarily interested in determining whether morphine would alter the response of a patient given intravenous fluid to overcome an existing oliguria or anuria. Thus it was not our purpose to study patients who were overhydrated and who would therefore exhibit a maximal diuresis.

His objection to comparing the effects of Pitressin injections on pregnant and non-pregnant women is certainly valid. We attempted only to compare the effect of morphine and Pitressin on the same pregnant woman in whom Pitressin caused a chloruresis and an antidiuresis for the first two hours. The limitations of our observations on the patients with diabetes insipidus were noted in our original communication, "while it is not possible to determine the exact amount of posterior pituitary still functioning in patients with diabetes insipidus, these individuals offer the only means of comparison with stalk-sectioned laboratory animal." The fact that oral fluids, except for those in the diet, were withheld for sixteen hours caused a reduction of the total twenty-four hour output of urine to that noted on the charts. Thus the test days did not reveal the severity of the diabetes insipidus.

The determination of urinary chlorides was included since de Bodo had reported a fifty fold increase in the concentration of chlorides in the urine and a twofold increase in the total excretion of chlorides in spite of the marked decrease in urine output in the first three hours following the injection of morphine in dogs. The lack of a chloruresis in our experimental subjects may be due to a species difference in response, although now de Bodo seems to minimize its significance. That morphine tends to produce an oliguria in normal pregnant and in nonpregnant women is in complete accord with de Bodo's findings in dogs, despite differences in preliminary hydration and marked differences in dosage



# ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES\*

(Appears in January, April, July, October)

- American Gynecological Society.** (1876) *President*, Joseph Baer. *Secretary*, Norman F. Miller, 1313 East Ann St., Ann Arbor, Mich. Next meeting, May 11, 12, 13, 1950, The Greenbrier, White Sulphur Springs, Va.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons.** (1888) *President*, Samuel A. Cosgrove, Jersey City, N. J. *Secretary*, L. A. Calkins, University of Kansas Medical Center, Kansas City 3, Kansas. Annual meeting Hot Springs, Va., September, 1950.
- Central Association of Obstetricians and Gynecologists.** (1929) *President*, George Kamperman, Detroit, Mich. *Secretary-Treasurer*, John I. Brewer, 24 West Ohio St., Chicago 10, Ill. Annual meeting to be held Thursday, Friday, and Saturday, Sept. 21, 22, and 23, 1950, at the Hotel Schroeder, Milwaukee, Wis.
- South Atlantic Association of Obstetricians and Gynecologists.** (1938) *President*, C. J. Andrews, Norfolk, Va. *Secretary*, E. D. Colvin, 1259 Clifton Road, N.E., Atlanta, Ga. Next meeting, Feb. 9, 10, and 11, 1950, Hotel Roanoke, Roanoke, Va.
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, William F. Mengert, Dallas, Texas. *Secretary*, A. B. Hunt, Mayo Clinic, Rochester, Minn. Annual meeting June, 1950.
- New York Obstetrical Society.** (1863) *President*, Albert H. Aldridge. *Secretary*, Claude E. Heaton, 205 East 69th St., New York 21, N. Y. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia.** (1868) *President*, Newlin F. Paxson. *Secretary*, George A. Hahn, 255 S. 17th St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society.** (1878) *President*, Eugene A. Edwards. *Secretary*, Edward M. Dorr, 30 N. Michigan Ave., Chicago 2, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society.** (1890) *President*, Henry S. Acken, Jr. *Secretary*, J. Edward Hall, 429 Clinton Avenue, Brooklyn 5, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society.** (1929) *President*, Houston S. Everett. *Secretary-Treasurer*, W. Drummond Eaton, 11 E. Chase St., Baltimore 2, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.
- Cincinnati Obstetrical Society.** (1876) *President*, Edward Friedman. *Secretary*, Lester J. Bossert, 2404 Auburn Ave., Cincinnati 19, Ohio. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society.** *President*, Rudy F. Vogt. *Secretary-Treasurer*, Glenn W. Bryant, Louisville, Ky. Meetings fourth Monday of each month from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology.** *President*, Ronald Frazier. *Secretary-Treasurer*, Gifford D. Seitz, 919 Taylor St. Bldg., Portland 5, Ore. Meetings last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society.** (1934) *President*, R. A. D. Gillis. *Secretary*, Clarence H. Ingram, Jr., 902 Peoples East End Building, Pittsburgh 6, Pa. First Monday of October, November, December, January, February, March, April, and May.
- Obstetrical Society of Boston.** (1861) *President*, M. Fletcher Eades. *Secretary*, H. Bristol Nelson, 1180 Beacon Street, Brookline, Mass. Third Tuesday, October to April, Harvard Club.
- New England Obstetrical and Gynecological Society.** (1929) *President*, Arthur E. G. Edgelow, Springfield, Mass. *Recorder*, Carmi R. Alden, 270 Commonwealth Ave., Boston 16, Mass. Meetings held in May and December.
- Pacific Coast Obstetrical and Gynecological Society.** (1931) *President*, Philip H. Arnot. *Secretary-Treasurer*, R. Glenn Craig, 490 Post St., San Francisco, Calif.
- Washington Gynecological Society.** (1933) *President*, George Nordlinger. *Secretary*, Stafford W. Hawken, 1150 Connecticut Ave., N.W., Washington, D. C. Fourth Saturday, October, November, January, March, May.
- New Orleans Obstetrical and Gynecological Society.** (1924) *President*, Conrad G. Collins. *Secretary*, E. W. Nelson, 1407 S. Carrollton Ave., New Orleans, La. Meetings held October, November, January, March, and May.

\*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the Society's name is the year of founding.

ease of withdrawal in the event of adverse effects. The principal effect obtained following intravenous use is that of accentuating a normal physiological gradient of activity from the fundus toward the lowermost part of the uterus (Hellman, Harris and Reynolds, 1949).

The necessary precautions to safeguard against too great a uterine response at the commencement of the intravenous drip include the following steps:

1. An observer should listen frequently to the fetal heart.
2. One operator should adjust the flow critically from zero to the desired frequency per minute. In so far as possible, adjustment of the drip should be made prior to the venous infusion in order to maintain a slow minimal rate of injection.
3. A shut-off valve near the needle should be used.
4. Standardization of needle size, length of tubing, and critical adjustment of the drop control device for complete control with respect to constancy and size of the drop are important.
5. A recorder of uterine contractility should be used to confirm the fact that a spasm of the upper part of the uterus is not elicited. If such a response occurs, the observer is warned and the record gives proof of subsidence of the danger following withdrawal of the Pituitrin.

These observations were made during a study currently in progress at Cumberland Hospital, conducted jointly by the Department of Embryology, Carnegie Institution of Washington, Baltimore, and the Department of Obstetrics and Gynecology, Cumberland Hospital, Brooklyn, N. Y. This work is aided by a grant from the Kate Lubin Research Foundation, Inc. The participants in this study include Samuel R. M. Reynolds, Ph.D., Richard Waltman, M.D., Barnet Delson, M.D., Leslie Tisdall, M.D., and the undersigned.

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4. Stone, M.: AM. J. OBST. & GYNEC. In press.
5. Theobald, G. W., Graham, A., Campbell, J., Gange, P. D., and Driscoll, W. J.: British M. J. 2: 123, July 17, 1948.

### Erratum

On page 1039 of the June, 1949, issue of the JOURNAL, in the article on "Nutrition and Human Reproduction: An Historical Review," by Robert D. Mussey, the word "colored," referring to drawings in the *Rosengarten*, 1513 edition, should be omitted.

- Omaha Obstetrical and Gynecological Society.** (1947) *President*, Harley E. Anderson. *Secretary*, Donald C. Vroman, 813 Medical Arts Bldg., Omaha 2, Neb. Meetings held third Wednesday in January, March, May, September, November.
- Oklahoma City Obstetrical and Gynecological Society.** (1940) *President*, John W. Records. *Secretary-Treasurer*, Henry G. Bennett, Jr., 800 Northeast 13 Street, Oklahoma City 4.
- Cleveland Obstetrical and Gynecological Society.** (1947) *President*, Robert E. Faulkner. *Secretary*, G. Keith Folger, 10515 Carnegie Ave. Meetings on fourth Tuesday of September, November, January, March, and May at University Club, 3813 Euclid Ave., Cleveland 15, Ohio.
- New Jersey Obstetrical and Gynecological Society.** (1947) *President*, Herschel Murphy. *Secretary*, Benjamin Daversa, Spring Lake, N. J. Meetings semiannually.
- Honolulu Obstetrical and Gynecological Society.** (1947) *President*, K. S. Tom. *Secretary*, S. Nishijima, 1221 Victoria St., Honolulu, Hawaii. Meetings third Monday of each month, Mabel Smyth Building.
- Oregon Society of Obstetricians and Gynecologists.** *President*, Gerald Kinzel. *Secretary-Treasurer*, Theodore M. Bischoff, 529 Mayer Bldg., Portland 5, Ore. Meetings held on third Friday of each month from October to May.
- National Federation of Obstetric-Gynecologic Societies.** (1945) *President*, Ralph E. Campbell. *Secretary*, Woodard D. Bencham, 429 Hutchinson Memorial Bldg., New Orleans 13, La.
- Dayton Obstetrical and Gynecological Society.** (1937) *President*, A. D. Cook. *Secretary*, L. O. Frederick, 413 Third National Bldg., Dayton 2, Ohio. Meetings, third Wednesday monthly from September through June at the Van Cleve Hotel.
- Dallas-Fort Worth Obstetric and Gynecologic Society.** (1948) *President*, Asa A. Newsom. *Secretary*, A. W. Diddle, 2211 Oak Lawn Ave., Dallas 4, Texas. Meetings in spring and fall.
- Queens Gynecological Society.** (1948) *President*, Edward C. Veprovsky. *Secretary*, George Schaefer, 112-25 Queens Blvd., Forest Hills, N. Y. Meetings held second Wednesday in February, April, October, and December, at the Queens County Medical Society Bldg.
- Mississippi Association of Obstetricians and Gynecologists.** (1947) *President*, R. A. Street, Jr. *Secretary*, William Weiner, Barnett-Madden Bldg., Jackson, Miss. Meetings held semiannually.
- Florida Obstetrical and Gynecological Society.** *President*, Charles J. Collins. *Secretary*, Dorothy D. Brame, Orlando, Fla. Next annual meeting, Belleair, April 10, 1949.
- South Carolina Obstetrical and Gynecological Society.** (1946) *President*, J. Decherd Guess. *Secretary*, Arthur L. Rivers, 231 Calhoun St., Charleston, S. C. Meetings held in spring and fall.
- Buffalo Obstetrical and Gynecological Society.** (1946) *President*, W. Herbert Burwig. *Secretary*, Clyde L. Randall, 925 Delaware Avenue, Buffalo, N. Y. Meetings held on the first Tuesday of October through May at the Saturn Club.
- El Paso Gynecological Society.** (1948) *President*, Gerald H. Jordan. *Secretary-Treasurer*, Gray E. Carpenter, 303 N. Oregon St., El Paso, Texas.
- Kentucky Obstetrical and Gynecological Society.** (1947) *President*, W. O. Johnson. *Secretary*, Edwin P. Solomon, 910 Heyburn Bldg., Louisville, Ky.
- Indianapolis Obstetrical and Gynecological Society.** (1947) *President*, David L. Smith. *Secretary*, Sprague H. Gardiner, 314 Hume Mansur Bldg., Indianapolis 4, Ind. Meetings held in January, April, and October.
- Houston Obstetrical and Gynecological Society.** (1939) *President*, John A. Wall. *Secretary-Treasurer*, Herman L. Gardner, Hermann Professional Bldg., Houston 5, Texas. Meetings held second Tuesday of each month except July, August, and September.
- Iowa Obstetric and Gynecologic Society.** *President*, J. H. Randall. *Secretary*, William C. Keettel, Iowa City, Iowa.

- St. Louis Gynecological Society.** (1924) *President*, A. N. Arneson. *Secretary*, Paul F. Fletcher, 634 North Grand Ave., St. Louis 3, Mo. Meetings second Thursday, October, December, February, and April.
- San Francisco Gynecological Society.** (1929) *President*, Albert M. Vollmer. *Secretary*, Donald W. de Carle, 2000 Van Ness Ave., San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists.** (1930) *President*, Julius McIver, Dallas. *Secretary*, George F. Adam, 4115 Fannin St., Houston 4, Tex. Annual meeting, Dallas, Texas, September, 1949.
- Michigan Society of Obstetricians and Gynecologists.** (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President*, O. W. Picard. *Secretary*, Carl F. Shelton, 910 David Broderick Tower, Detroit 26, Mich. Meetings first Tuesday of each month from October to May (inclusive).
- Central New York Association of Gynecologists and Obstetricians.** (1938) *President*, Louis G. Fournier. *Secretary*, Merton C. Hatch, Medical Arts Bldg., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.
- Alabama Association of Obstetricians and Gynecologists.** *President*, Gilbert F. Douglas. *Secretary*, Hunter Brown, 1922 South Tenth Ave., Birmingham, Ala.
- San Antonio Obstetric Society.** *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.
- Seattle Gynecological Society.** (1941) *President*, Donald J. Thorp. *Secretary-Treasurer*, Charles D. Kimball, 734 Broadway, Seattle 22, Wash. Meetings held on third Wednesday of each month, Washington Athletic Club.
- Denver Gynecological and Obstetrical Society.** (1942) *President*, Lyman W. Mason. *Secretary-Treasurer*, Jack M. Simmons, Jr., 638 Republic Bldg., Denver 2, Colo. Meetings held first Monday of every month from October to May (inclusive).
- Wisconsin Society of Obstetrics and Gynecology.** (1940) *President*, Henry A. Sincok. *Secretary-Treasurer*, Edith McCann, 425 East Wisconsin Ave., Milwaukee 2. Meetings held in May and October.
- San Diego Gynecological Society.** (1937) *President*, P. L. Martin. *Secretary*, Albert P. Kimball, 233 "A" St., San Diego, Calif. Meetings held on the last Friday of each month.
- North Dakota Society of Obstetrics and Gynecology.** (1938) *President*, H. A. Wheeler, Grand Forks. *Secretary*, C. B. Darner, Fargo, N. D.
- Virginia Obstetrical and Gynecological Society.** (1936) *President*, Walter McMann. *Secretary-Treasurer*, L. L. Shamburger, State Health Department, Richmond, Va. Next meeting not announced.
- Columbus Obstetric and Gynecologic Society.** (1944) *President*, Wayne Brehm. *Secretary*, Zeph J. R. Hollenbeck, 9 Buttles Ave., Columbus, Ohio. Meetings held fourth Wednesday of each month.
- Naussau Obstetrical Society.** (1944) *President*, Robert S. Millen. *Secretary-Treasurer*, Peter La Mariana, Williston Park, L. I., N. Y. Meetings, bimonthly from October to May.
- Bronx Gynecological and Obstetrical Society.** (1924) *President*, Charles W. Frank. *Secretary*, Benjamin Karen, 1100 Grand Concourse, New York 56, N. Y. Meetings, fourth Monday monthly from October to May.
- Washington State Obstetrical Society.** (1936) *President*, John H. Fiorino, Everett. *Secretary*, C. Wendell Knudson, Medical and Dental Bldg., Seattle, Wash. Meetings, first Saturday of April and October.
- Kansas City Obstetrical and Gynecological Society.** (1922) *President*, Harold V. Holter. *Secretary*, William C. Mixson, 320 W. 47th St., Kansas City, Mo. Meetings, last Thursday, September, November, January, and March; first Thursday, May, University Club.
- Los Angeles Obstetrical and Gynecological Society.** (1914) *President*, A. M. McCausland. *Secretary-Treasurer*, Gordon Rosenblum, 6333 Wilshire Blvd., Los Angeles 36, Calif.
- North Carolina Obstetrical and Gynecological Society.** (1932) *President*, Wallace B. Bradford. *Secretary*, Richard B. Dunn. Meetings semiannually.
- The Society of Obstetricians and Gynecologists of Canada.** (1944) *President*, H. B. Atlee. *Secretary*, K. M. Grant. Annual meeting, June, 1950.
- Akron Obstetrical and Gynecological Society.** (1946) *President*, George A. Palmer. *Secretary-Treasurer*, Alven M. Weil, 1030 First National Tower, Akron 8, Ohio. Meetings held third Friday of January, April, July, and October, City Club of Akron, Ohio, Bldg.
- Minnesota Obstetrical and Gynecological Society.** *President*, Russell J. Moe. *Secretary*, John Haugen, 100 E. Franklin, Minneapolis, Minn. Meetings held spring and fall.
- Miami Obstetrical and Gynecological Society.** (1946) *President*, Homer L. Pearson. *Secretary*, John D. Milton, 1104 Huntington Bldg., Miami, Fla. Meetings, second Thursday in January, March, May, and November.

much vacillation I finally decided on a topic which seemed timely and of common interest and with which I have a better than speaking acquaintance. I shall inflict upon you some of my views on the trends in cancer research and on certain teaching problems concerned with cancer. Do not expect to hear an erudite recitation of the many facets of investigation nor a learned review of the efforts of the many who have searched for an answer to a timeless enigma. My remarks simply are reflections that I like to air and I could not think of a better opportunity than to do this among men whom I consider broadminded and thoroughly conversant with the subject matter of this address.

I believe it not presumptuous to state that there is a need for a dispassionate re-evaluation of our thinking on the broader aspects of cancer research because there is ample evidence that it is drifting into a world of its own, steadily expanding in scope, but equally fast moving away from the human problem. The late James Ewing said some ten years ago that "the ramifications of the interest in cancer, which reach into many branches of human knowledge, form a broad basis which assures sound progress, but at the same time become a definite menace, because when every type of investigation claims a relation to cancer, the resources become dissipated over too vast a territory and are apt to lose practical value." This conclusion still holds.

As one reads the important reviews of cancer research, one cannot escape the feeling that there is serious doubt in the minds of many regarding the ultimate value of the present trends in cancer research and that a new approach, more closely related to the human problem, must be found. I do not mean to be critical but it seems to me that research not only must make an inventory of its achievements on the basis of an objective evaluation, but that also we should inquire critically whether the public interest in cancer research is intelligent or largely emotional and uncritical, just as we should inquire quite as critically whether the resources that are now being poured into this field are wisely invested or largely wasted in terms of service to humanity.

There is good reason to believe that a considerable portion of cancer research is not efficiently planned and is largely of the variety that Lord Chesterton described as the effort of the blind man looking into a dark closet for a black hat that is not there. The usual defense for this type of research is that it deals with pure science and that as such it adds to the sum total of basic knowledge. Some, no doubt, is, but much more is not, but constitutes solely an irrelevant variety of sporadic exploits largely based on that forlorn hope that some great discovery may result from it purely by accident. Yet, time and experience have proved conclusively that only skillful planning based on broad scientific experience and endless perseverance can produce the really worth-while contributions to the knowledge of cancer. Most of the work of the other variety has gone by the board and has served no other purpose than to clutter up the literature. At best, cancer research of the serious variety is painfully slow in yielding important results because even under the

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### ADDRESS OF THE PRESIDENT\*

LUDWIG A. ENGE, M.D., SAN FRANCISCO, CALIF.

THERE is no accounting for the twists of fate that affect our lives. Here I find myself the President of this distinguished Society, yet I still cannot figure out why you should have been so unaccountably partial in your choice. My incoherent remarks of acceptance at last year's meeting were about as inadequate in expressing my appreciation as they are now in thanking you for having accorded to me the privilege of letting me share in the guidance of this distinguished Society. I hope you will believe that my thanks, though still inadequate, nevertheless are most sincere.

Since it is the traditional obligation of the President to deliver an address, I bow to the inevitable, though I should prefer to remain silent, for, as the Japanese saying goes, the silent man is best to listen to. My predecessor brought you up to date on the state of the Society in his erudite address and there is little to add for the past year that warrants inclusion here except to record the election of three Fellows to active membership: A. N. Arneson, John Parks, and Herbert E. Schmitz, and the passing of seven of our Fellows who have left an indelible impression on the pages of our annals. I report with deep regret the death of Thomas Watts Eden, Klaas DeSnoo, and George L. Streeter, Honorary Fellows; Jennings C. Litzenberg, Franklin S. Newell, and Howard C. Taylor, Life Fellows, and Henricus J. Stander, an active Fellow.

I have not found it simple to select a subject of general interest which has not been discussed wholly or in part by other Presidents of this Society. After

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\*Presented at the Seventy-Second Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 17, 1949.

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NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

in our treatment centers if these hormones necessarily were primary factors in carcinogenesis, as we have been told many times by some of those whose whole concern is the laboratory animal? Or, could it be that in terms of human life the time of observation elapsed is too short as interpreted in terms of small animal experimentation? Here is another gap between pure laboratory research and clinical experience that must be bridged by the trained research worker in conjunction with the clinician, and it can only be bridged through an approach of the human problem. It may prove eminently more complicated and cumbersome to carry out this task, but it should prove definitely more useful to the human race than the relatively uncomplicated and very comfortable approach through the laboratory animal. The richest fuel for creative power comes from firsthand information. Somebody, I do not recall who, once said that we surely will gain more from milking a cow than from looking at the milk bottles on the window sill, and that goes for a lot of present-day cancer research. To be sure, I am not deprecating fundamental research for I fully appreciate the heroic efforts of the really serious, well-trained, and experienced investigators who forsook the fleshpots for the sake of science, and besides, I speak from within the ranks, having spent a large part of my life in the sanctity of the laboratory. But the more I see and hear of present trends in cancer research, the more I become convinced that the ivory-tower attitude many research workers assume should be abandoned in favor of a resurgence toward the study of man. There can be no doubt that we need the help of the trained research workers in solving our cancer problems, but we need a much closer cooperation between the laboratory and the clinical fields than has been achieved up to now. Where such cooperation exists, it has yielded rich returns. I only need to point at the development of the cytologic screening methods which resulted from the mutual efforts of an anatomist and a gynecologist.

I must not prolong this discussion by a recital of the various cancer problems that confront us for they are thoroughly familiar to you. My aim in bringing my thoughts to you on the present trends in cancer research is to provoke a discussion in the hope of stimulating a closer approach between research and clinical practice. Anybody interested in the study of cancer must realize that we are faced constantly with the workings of two lines of thought. One is based on the struggle of experience against theories and the other is the use of the experimental method in determining the true significance of experience. There is as great a need for theoretical research now as there always has been, but some attempt must be made to strike a balance once in a while or clinical knowledge and fundamental research ultimately will become unrelated. Lancelot White, the Scottish physicist, once said that "the scientist must go out in search of facts, but he must also sometimes pause to arrange them." And, elsewhere, he added that every great movement is in essence simple and that resistance serves to challenge the new to greater efforts of discipline and achievement. To which I add that we do not live just to have experience but to learn from it. Living in a world of living men, we must have

most propitious conditions there are limits to all efforts, which are beyond our control, because the system with which we work is inconstant and subject to a limitless variety and variability of the aggregates to be studied and to be correlated. Irrelevant research, therefore, should be discouraged for there is no reason to believe that the present state of the knowledge of cancer justifies the hope that a sensational solution is just around the corner. No doubt we need sound fundamental research to understand basic phenomena, but I believe, too, that the time has come to ask those engaged in the study of the pure sciences to lend a more helpful hand with the human problem because our efforts to stem the tide of malignant disease rapidly are approaching an impasse.

To illustrate my contention that cancer research must take a different attitude toward the human problem, I shall cite briefly what has happened to the study of irritation in relation to cancer. The idea that irritation might cause cancer is very ancient and antedates Hippocratic teachings. However, the basic theory of irritation as we know it stems from Galen who formulated it on the basis of his own observations and deductions. Quite naturally twenty centuries have modified the *modus operandi* of his thinking, yet a vast amount of experimental inquiry has not brought us materially closer to the solution of the human problem. This is forcefully brought out when one evaluates critically the meaning of the carcinogens. We now know many of such substances and we are familiar with their behavior in animal experimentation. Yet, the vast effort necessary to produce this knowledge has failed to give us even as little as a hint how to solve our clinical problem for we still do not know, for instance, why aniline dyes create cancer of the bladder in man. Fundamental research has been content with producing cancer of all sorts in small laboratory animals with a variety of unrelated chemical compounds, yet it has made little or no effort to determine the nature of the specific irritant that produces bladder cancer in aniline dye workers. That is what I mean by saying that fundamental research is drifting into a world of its own and away from the human problem. If all of the hundreds of carcinogens now listed actually were factors in the production of human cancer, I fear that by now most of us should have succumbed to the disease.

We have a similar problem confronting us now in our own specialty. I have reference to the possible relation of the estrogens to cancer. This subject certainly is in a highly controversial state. A vast amount of fundamental research has been done, largely on small laboratory animals, yet it has served to obscure rather than to clarify the problem, and it also has done much to add further fuel to the already upset emotions of the public in their thinking on cancer. The immense amount of human cancer material flowing through the clinics of the world hardly has been tapped for extensive hormone studies. The few limited studies undertaken are at variance with most of the conclusions derived from the study of small laboratory animals. Yet, estrogens have been injected, implanted, and fed to human beings for nearly thirty years. Should we not encounter by now some increase in certain forms of cancer



for student teaching. The vast mass of cancer research, with a few outstanding exceptions, is not immediately usable for such teaching since such knowledge is notably irrelevant in its relation to clinical practice. It would be disastrous to burden the student with the many fanciful flights into abstract research when already he is so very close to his capacity of coping with a huge and often indigestible amount of reading. The U. S. Public Health Service which also is interested in placing funds for the improvement of teaching facilities wisely has refrained up to now from issuing an official blueprint for planning a cancer teaching program but has assumed the attitude that for the present each school must work out its own program in whatever manner it might fit local needs and facilities. And that is as it should be under the rules of academic freedom in any true democracy. This rather unusual attitude on the part of a Federal agency entrusted with the dispersal of public moneys is refreshing and most commendable, and I like to believe that this attitude is as sincere as it is far-sighted. I do not like to think that any agency holding the strings to a well-lined purse is desirous of injecting itself into our planning and thinking because we are desperately in need of additional funds to enlarge existing diagnostic and therapeutic facilities, but at times I sense such an attitude though I fervently hope that I am mistaken. The tendency to overorganize medical teaching is a curse in itself and should be resisted before it brings other evils detrimental to academic freedom. To submit to the dictates of an outside agency just for the sake of much needed financial support beyond the accountability for moneys received would be intolerable and certainly destructive to the thinking of free men and women. I leave it to you to judge for yourself what stand to take in this controversy.

It is rather interesting to learn what outsiders think of our ways of teaching medicine. Recently, I read in *Cancer News* (January, 1949) a reference to certain schemes of teaching. It was pointed out that because various segments of information are not integrated, the medical student graduates without obtaining the necessary composite picture of cancer and with only a fragmentary knowledge of the basic diagnostic methods and recommended forms of treatment. Because this journal is widely read such a statement should not remain unchallenged since it implies indifference on the part of the teaching profession toward a very pressing problem. If this statement were based on irrefutable evidence I should be the first to acknowledge its merit and promptly take a hand in initiating a move to correct the evil. Although I can speak only for our far-Western medical schools whose quality of teaching I am thoroughly familiar with, I would like to go on record that the statement cited is not based on fact and exhibits a lack of insight into the teaching problems and curricula offered by all progressive medical schools. There is no denying that there always is room for improvement, but what serious teacher would ever stop at making improvements according to circumstances and whenever new discoveries warranted their acceptance? Quite naturally, teaching methods vary to some extent in different institutions and the views of teachers vary according to personal experience, but in principle the philosophy behind

a horizontal view of life; living at a point on a long road of research we want a vertical view of results. The individual concerned with the study of cancer must take his place where the horizontal and vertical views cross, somewhat like locating a target through a bomb sight.

Another problem of considerable interest to me concerns itself with the teaching of cancer to medical students as well as to graduates. I feel sure that all of you are aware that considerable discussion is now under way within and between teaching institutions for the purpose of reviewing methods used in the teaching of cancer. The suggestion has been made that all teaching of cancer might best be handled by those who devote their entire time to the study and treatment of malignant diseases. In fact, in some thirteen medical schools departments of oncology have been organized. This tendency to segregate cancer from the body of medical teaching is looked upon with favor in various quarters actively engaged in the collection and distribution of funds to be used in the fight against cancer. The U. S. Public Health Service, acting as the guardian of Federal money set aside by Congress for such purpose, has requested that grants to medical schools should be the concern of a "cancer coordinator," which I picture as something of a cross between a major-domo of the faculty possessed of an encyclopedic knowledge and a sort of commissar empowered to direct our thinking on the subject of cancer. There actually exists now an organization of such cancer coordinators who meet to exchange ideas and formulate policies to be submitted to their respective faculties. The upshot of a recent meeting was that while medical schools have different teaching programs the common emphasis is about the same in all programs. To arrive at this momentous conclusion valuable time and government money were spent to no purpose except to discover what long since has been common knowledge among medical teachers.

In conjunction with the proposal to institute cancer coordinators there also has been some talk about the advantages of "vertical" versus "horizontal" teaching; the former to mean that all teaching of cancer is to be delegated to a coordinator or a so-called cancer expert who will treat the subject as a distinct specialty; the latter to mean that all teaching of cancer shall remain as heretofore part and parcel of the broad teaching of medicine and surgery, or in other words, that cancer shall be taught as it concerns the patient and not just as it pertains to the organ. It is my understanding that under the "vertical" scheme of teaching an otherwise competent and experienced clinician may tell all there is to know about his particular field except cancer. When that subject comes up for discussion he must yield to the cancer expert who then teaches that subject as something entirely apart. I do not know from what quarter such thinking has emanated, nor is that a matter of importance, for the fallacy of "vertical" teaching will be recognized by all experienced medical teachers as curricular gadgetry. Advances in the knowledge of the nature of cancer and its treatment are coming along at snail's pace; I cannot conceive of a seasoned and accomplished medical teacher incapable of keeping abreast with factual cancer knowledge such as is usable

ishing returns'' with the inevitable consequence of reducing the quality of teaching. I call on all those who take great pride in modern methods of medical teaching to resist the attempts of outside agencies to tempt medical faculties with financial baits in exchange for an increase in the present size of classes, unless certain prerequisites have been satisfied. With the limitation of clinical material and the scarcity of trained teachers, money alone and increased physical facilities evidently are not the answer. Before agreeing to an increase in the enrollment to our medical schools, we first must improve the material status of the medical teachers in order to attract enough of the right individuals trained and experienced in proper teaching methods. Then we must increase our clinical material sufficiently through free care and free hospitalization which many institutions are unable to afford for obvious reasons. Only then should we give thought to an increase in our enrollments. Since it is all a matter of finances a good share of the available moneys now diverted to irrelevant cancer research could be employed to better advantage if used for clinical purposes. If there were a place for a cancer coordinator it should be there.

We are living in a very critical period so far as the future of medical teaching is concerned. I am sure that you, too, have been wondering what would happen to medical teaching should medicine become socialized with a free choice of doctors. I am convinced that it would reduce our clinic material to a negligible quantity, for the average American citizen most certainly would abandon the teaching clinic in favor of private care. The public, no doubt, will think this a good argument for socialized medicine, and in the light of American thinking of equality and human rights it is, yet, in the light of medical teaching it would result in a return to archaic methods of instruction which would set us back fifty years. It would call for a complete reorganization of medical teaching probably controlled by government decree.

So far as the present status of the teaching of cancer to medical students is concerned, I am content that it is in line with all other medical teaching and that it is well integrated with the sum total of teaching matter. I sincerely believe that it is practical within the limitations already discussed and that it is sanely presented within the scope of undergraduate instruction. Therefore, I urge that the teaching of cancer be not dissociated from the general body of medical instruction by fanciful schemes emanating from pressure groups but that it be left in its logical position in the time-tried method of horizontal teaching.

Postgraduate teaching of cancer is undertaken primarily for the benefit of the busy general practitioner who represents the first and most important line of defense against all diseases. It has been stressed that because of the time lost between the recognition of cancer and the institution of efficient treatment the cure rate cannot improve materially until this time interval has been reduced drastically. Postgraduate teaching hopes to eliminate this factor with the aid of various agencies and state and county medical societies through various approaches to the problem.

the teaching differs but little since its common aim is to make the student conscious of disease in all its form as well as proficient in the fundamentals of diagnosis and treatment. This very same principle applies to the teaching of cancer. What the public fails to understand is that in the short span of four years we cannot turn out a finished technical expert experienced not only in the treatment of all diseases but also possessed of the judgment of a sage. Evidently, our critics fail to understand that there is not only a limit to the volume of teachable material but also a limit to the individual capacity of the average student to absorb and digest what is being taught and that even carefully selected students are subject to mental fatigue in spite of youth and physical stamina. Yet, it is exactly that individual capacity to learn and to retain which, in the end, largely determines the ultimate performance of a physician. Even under the best of teaching conditions the most that can be hoped for is that every student at the end of the prescribed years of learning has been grounded sufficiently in the fundamentals on which to build the edifice of his future performance in medical practice. We cannot produce experts in any branch of medical practice in four short years and the public should be told about this often enough to realize the limitations of the best of teaching schemes.

There is another important factor in teaching which the public does not understand and that is that the ultimate result of modern teaching in medicine is not dependent upon bigger and better buildings but upon the limitations in the number of students to be taught in conformity with the clinical material necessary for good teaching and the size and quality of the faculty available to convey information to the student in such a manner that what is taught will make a lasting impression. Yet there is constant pressure being brought upon medical schools to enlarge the size of their classes without due regard to the factors cited. Good teachers in medicine are becoming scarce because like all other teachers they are underpaid on the whole. Yet, it is only a good teacher who can establish a satisfactory student-teacher relationship which is the acme of sound teaching. Large classes are detrimental to a close relationship between teacher and student. The average layman takes it for granted that any doctor of medicine can be a teacher and hence there should be no shortage, and I dare say that many doctors of medicine labor under the same delusion. But I know from long experience that this is just wishful thinking on the part of those who would like to sun themselves in the reflected glory of a teaching institution. Teachers are born, yet they still must learn the mechanics and philosophy of teaching before their teaching achieves the soundness that removes it from the level of textbook recitation. The old style lecture is a matter of the past. Its place has been taken by teaching methods which more closely approach the spirit of the Socratean dialogue. This in turn calls for teachers possessed of more than book learning and at the same time capable of imparting the meaning of knowledge to students. Effective teaching in that sense limits the number of students to be taught. Any deviation from this principle invites the workings of the "law of dimin-

that can be read just as readily at home, provided the art of reading has not been lost? I am certain that it is not. Theologians have pointed out since time immemorial that professing to a creed and living one's religion are two very different moral entities of which only the latter is of true importance. In medicine we deal with exactly the same balance of values. There is a wide difference between practicing the art of healing and living the practice of medicine. One is the means to an end but the other is the living up to an ideal which is more important whatever way one looks at it. I sincerely believe that while there is constant need for technical improvement there is even greater need for a re-evaluation of individual integrity and the implied obligations concomitant with the practice of medicine. Unless we teach the broader philosophic ideals of practice in conjunction with the technical details, I fear that postgraduate sessions on the whole have missed a golden opportunity. I believe that there is great need for emphasizing that whoever takes up the burden of safeguarding life, limb, and human happiness must do so solely in the best interest of the patient. If we earnestly strive to put over this message, I am at least hopeful that it will aid in improving the thinking on cancer. If, on the other hand, we are content with barnstorming merely to stuff the practitioner with a multitude of technical facts and statistics and dazzle him with visual demonstrations, which often leave him bewildered, we have not conveyed to him the true message of improving the diagnosis and treatment of cancer.

I should have liked to touch on several other phases of the cancer problem, such as the education of the public and the meaning of statistics, but I must not exhaust your patience. I regret that there can be no discussion from which I could profit. However, the writing of this address has helped me immeasurably to clarify my own thinking. In presenting it to you I have been guided by Paul's advice to the Corinthians: "Unless ye utter by the tongue speech easy to be understood, how shall it be known what is spoken? For you shall have spoken into the air."

2000 VAN NESS AVENUE

Postgraduate instruction in cancer is relatively uncomplicated as it relates to residency training in approved hospitals where adequate time and material and experienced supervision give the graduate every opportunity to reach a high degree of proficiency in technical matters and where the long association with earnest and scholarly staff members implants and germinates the seeds of thirst for knowledge.

The situation, however, is vastly different for that large group of medical graduates who by dint of circumstances must enter into the practice of medicine after relatively short periods of hospital training. Yet, this group constitutes by far the greater mass of practitioners on whom the public depends for the safeguarding of life and health. The breadth of general practice puts not only an immense physical burden upon the shoulders of these courageous men and women, but it also demands a range of knowledge often beyond individual capacity since even general practitioners are only human and often very tired humans. The often cited excuse that because many general practitioners, at best, see only an occasional case of cancer in many months and that, therefore, it should not be expected of them to be adequately experienced in the intricacies of the disease, of course, is no more tenable than failing to suspect the presence of any rare disease. It is a matter of mental discipline to keep alert rather than a matter of technical experience alone. If the humdrum of daily routine and the material success of practice have not entirely destroyed the intellectual capacity of a practitioner, he certainly must have preserved enough of the fundamentals of his teaching and training to be able to measure his own knowledge, and if found not to be adequate, to venture forth in search of additional information. Are we as teachers responsible to keep forever on the trail of our graduates in order to keep them up to the level of expected performance, or is the individual responsible to achieve such ends by his own efforts? I believe that the latter is the real crux of the whole problem. Other professions do not tag after their members in order to spoonfeed them, yet we do because we are keenly aware of our responsibility to humanity. For some time I have been wondering if we are achieving actually what we hope to achieve by our present methods of postgraduate teaching.

As you well know small bands of zealous practitioners, many of them professional medical teachers, have traveled about the land far and wide to enlighten the busy doctor on the subject of cancer. Conferences, refresher courses, formal postgraduate sessions solely devoted to cancer are held in many centers at frequent intervals. By and large, this form of postgraduate teaching is sound in spite of its limitations. I have participated in and followed this trend of delivering knowledge in small packages for some years, but I also have become convinced gradually that the dispensing of technical knowledge alone is not enough to achieve our ends. Do the participants actually return to their own spheres of activity mentally prepared to feed the fire kindled by the spark of a graduate session? Has it really awakened a new interest in the potential dangers of delayed diagnosis? Is it just enough for us to present over and over again the details of diagnosis and treatment

was positive in 35, or a percentage error of 12.5 per cent. In the same group of cases, the biopsy failed to discover the preinvasive lesions in 12, or 30.0 per cent. Thus, in our experience, the routine vaginal smear is more accurate than routine biopsy in the diagnosis of preinvasive carcinoma of the cervix. The major reason for the failure of biopsy to reveal a higher percentage of accurate diagnoses in carcinomas is that, if the carcinoma is small and the cervix presents no abnormalities grossly, it is extremely difficult to choose accurately the site of biopsy. Obviously, if multiple biopsies are taken, the diagnostic accuracy of the biopsy method will be increased. However, with single routine biopsies, the accuracy of diagnosis has not been as high as that of single routine vaginal smears in early carcinoma of the cervix. A real advantage of the cytologic technique is that the diagnostic accuracy is greater in the early carcinomas than in those which are far advanced. The cytologic method depends on the desquamation of well-preserved cancer cells. If the tumor is far advanced, the surface may be necrotic and no cancer cells will be picked up on the smear. On the other hand, early tumors have a well-nourished surface, and the cancer cells which desquamate are in considerable numbers and are readily identified. An additional advantage is that the vaginal secretions contain representative cells from all surfaces of the genital tract so that the region examined is not limited by the size or location of the sample taken.

There has been much discussion of the possible use of the vaginal smear in a widespread screening of well women. We have not had any experience with wide-scale use of the method in this way, but gradually more routine smears have been sent to the laboratory. We have been impressed with the number of early and often symptomless carcinomas discovered in even small-scale screening. In 305 cases screened in the office of one of our medical colleagues,<sup>5</sup> five carcinomas were discovered, four of them cervical. Three of these cases had no bleeding or discharge, and the cervix appeared normal to inspection. Case report:

M. G., aged 43 years.

Chief complaints: Diarrhea and arthritis. No bleeding or discharge.

Local examination: Cervix appeared lacerated.

Vaginal smear: Positive and consistent with squamous carcinoma.

Biopsy: Carcinoma in situ.

Operation: Radical hysterectomy with bilateral dissection of pelvic lymph nodes.

Pathologic report: Gross examination: Cervix appeared normal to inspection  
Microscopic examination: Squamous cell carcinoma in situ.

In a moderate screening test on all patients entering the Gynecologic Out Patient Department of the Massachusetts General Hospital, five early carcinomas of the cervix were found in 735 patients.

These figures are higher than those expected in screening all women. Lombard,<sup>6</sup> from the Massachusetts State Cancer Commission, reported an incidence of 0.2 per cent. Our figures of 0.7 per cent in contrast to the above, may suggest that, from a practical point of view, perhaps a higher percentage of unsuspected cases may be found in screening office patients or part of a hospital population than in wide-scale screening of well women.

We have found the vaginal smear of use in the routine follow-up of patients treated for malignant disease. In three instances, postradiation recurrences were detected though the patients appeared free of disease clinically. In each instance positive biopsies were only obtained when the adhesions at the vaginal apex were broken, the disease in all instances being behind the adhesions. One early postoperative recurrence was discovered by cytologic

## THE VALUE OF THE VAGINAL SMEAR\*

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*(From the Massachusetts General Hospital)*

THE Vincent Memorial Laboratory has used the vaginal smear as an aid in the diagnosis of uterine malignancy since 1942. This report is our experience with the method in this six-year period and a discussion of its application in carcinoma of the cervix.

The cytologic diagnosis of cancer is based upon the fact that both normal and cancer tissue shed cells continuously from their surface. There is evidence that the desquamation from malignant tissue takes place more rapidly than from normal tissue. Coman in 1944<sup>1</sup> in a unique way measured the force required to pull cells apart. The force required to separate normal cervical cells was ten times that required to separate the cells of squamous carcinoma of the cervix. This characteristic of cancer tissue facilitates the diagnosis of cancer by identification of exfoliated malignant cells. Though the normal cells are almost always in the majority, numbers of cancer cells usually desquamate, even in early lesions.

The method by which these desquamated cells are obtained, placed on a slide, and fixed, varies from laboratory to laboratory. Vaginal, cervical, endocervical, or endometrial smears may be done. Scraping of the cervix with a wooden spatula and then placing those cells on a slide has been advocated by Ayre.<sup>2</sup> Fixing a large mass of vaginal secretion and running the mass through the usual histologic technique for pathologic tissue had been advocated by Hunter.<sup>3</sup> Our experience has dealt almost entirely with the vaginal smear. We have used it almost exclusively since we felt that one of the great advantages of the method was the simplicity of obtaining material. To add additional equipment and complicate the process seemed to lessen this advantage. We have used the curved glass pipette and bulb to aspirate the secretions collected at the posterior fornix. In special cases all types of smears are done, but for routine purposes we have relied on the vaginal smear. All smears have been stained by the method of Papanicolaou.<sup>4</sup>

In a six-year period we have studied 8,133 cases by means of the vaginal smear. The statistics presented here are based on the *initial* smear. If, in a case of carcinoma, the first smear was negative and the second one positive, the case is catalogued as an error in diagnosis. If the statistics were based on individual smears, the accuracy would be much higher. In this period of time there have been 432 carcinomas of the cervix, 401 of these squamous and 31 adenocarcinoma. Ninety per cent have been diagnosed correctly by cytologic examination. Thus, the false negative figure in this group of cases is 10 per cent. Let us examine our results as to the accuracy of diagnosis in early carcinoma. In 40 cases of carcinoma in situ of the cervix, the initial vaginal smear

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minutes; others take considerable time. On the average, a well-trained technician can screen a slide adequately in ten minutes, yet this is only an estimate. The cost or time required per slide is not prohibitive and neither should prevent widespread application of the method. The most serious bottleneck is the lack of well-trained personnel.

We should like to emphasize that the vaginal smear is not a substitute for biopsy as a method of diagnosis of cervical carcinoma but is a complementary method. In 1948 one of us did a comparative study between the initial diagnosis by vaginal smear and by biopsy in 181 primary carcinomas of the cervix.<sup>7</sup> The vaginal smear was negative in 17, or 9.4 per cent; the biopsy in 19, or 10.5 per cent. Thus there was no significant difference. However, if both methods were used together, the diagnostic accuracy was 98.3 per cent since only three cases were missed by both methods. This indicates that neither method should be used to the exclusion of the other, and that if both methods are used together, the accuracy of diagnosis will be higher than if either one is used alone.

TABLE II PRIMARY SQUAMOUS CARCINOMA OF THE CERVIX (181 CASES)

INITIAL CYTOLOGIC REPORT	INITIAL BIOPSY REPORT	NO.	PER CENT
+	+	148	81.7
+	-	16	8.8
-	+	14	7.7
-	-	3	1.7
		181	99.9

Finally, a word should be said about the interpretation of reports of cytologic examination. Since there are 10 per cent of false negative reports in the cytologic diagnosis of cancer of the cervix, a negative vaginal smear does not rule out the presence of a carcinoma. If signs or symptoms suggest cancer, a negative cytologic report should not be considered seriously. A positive vaginal smear, however, is of extreme importance, and the physician is obligated to make an extensive search for the carcinoma. We do not advocate radical surgery or radiation treatment on the basis of a positive cytologic report, but believe that the positive vaginal smear should be confirmed by biopsy. In some instances this will require more than one biopsy, and a real effort must be made to confirm the cytologic finding. If the vaginal smear is used in this way, unsuspected early carcinomas of the cervix will be discovered.

With the curability of carcinoma of the cervix at its present low figure, we cannot afford to disregard any method which offers an additional opportunity to diagnose early carcinoma. The cytologic examination of the vaginal secretion deserves a place in every gynecologic clinic.

Conclusions

1. Cytologic examination of smears in the Vincent Memorial Laboratory since 1942 has proved of great value.

examination. In an evaluation of the status of the treated cancer patient, we feel the vaginal smear is an essential part, and do vaginal smears routinely on all patients entering the Gynecologic Tumor Clinic.

Of the 432 cases of cervical carcinoma diagnosed by vaginal smear, 38 or 8.7 per cent are considered to be unsuspected. Of these, 19 had no discharge or bleeding, and their cervixes appeared normal to inspection. The only reason for obtaining a biopsy in these patients was the positive cytologic finding. The remaining 19 had some symptoms which might have pointed toward malignancy, but the symptoms were minimal and rationally explained on some other basis, such as withdrawal bleeding after estrin therapy. We believe that, in these instances, the carcinoma would have been discovered much later if the cytologic examination of the vaginal secretion had not been used. Of the 38 cases which are considered unsuspected, 28 were carcinoma in situ, and 10 were invasive carcinoma. In our hands the cytologic examination of vaginal secretion has proved of value in the detection of early carcinoma in a limited screening of symptomless women and in the follow-up of treated malignancy.

What of the other side of the picture? How specific is the test? Are false positive diagnoses numerous? During the first year in which we interpreted vaginal smears, the false positive figure was 6.4 per cent. As shown in Table I, the error has been reduced until during the year of 1948, of 2,420 negative cases, only one case was called positive erroneously. This is a 0.04 per cent false positive error. The steady reduction in error can only be attributed to increased experience in differentiating atypical benign cells from carcinoma cells. In the past two years, we have not had a case in which the vaginal smear was positive and consistent with squamous carcinoma that has not been proved histologically to have been squamous carcinoma. The single false positive made in 1948 was thought to present the cytologic picture of an adenocarcinoma of the endometrium. With experience in the microscopic interpretation, the specificity of a positive diagnosis of squamous carcinoma is so high that a presumptive diagnosis of carcinoma must be made.

TABLE I

YEAR	NEGATIVE CASES	FALSE POSITIVES	PER CENT ERROR
1943	265	17	6.4
1944	875	15	1.7
1945	962	14	1.4
1946	1,292	18	1.4
1947	1,897	5	0.2
1948	2,420	1	0.04

The practical or economic aspects of the method must be considered. How much does it cost and how much time does it take? (The cost per slide to the patient is two to five dollars.) The major portion of the expense is salaries of technicians and this will vary with the amounts paid in salaries. The equipment needed for the method is limited and is not expensive. A figure between two and three dollars' cost per slide should be regarded as an estimate. The time required to study each slide is much more difficult to answer. Obviously, some smears may be called either negative or positive with assurance in a very few

of the hospital. The remaining 6,000 patients were seen in the various Health Maintenance-Cancer Detection Clinics sponsored by the Donner Foundation of Philadelphia. Our total number of "correct positives" and "correct negatives" in this very large group have not been accurately tabulated because of incompleteness of the follow-up to date. "False negatives," however, average 10 to 15 per cent. "False positives" are less than 1 per cent if we include the Health Maintenance-Cancer Detection Clinics, but 1.5 to 2 per cent on selected patients, due probably to the high percentage of benign lesions seen.

It is true, as the author states, that the smear tends to be more valuable in early than in advanced lesions; hence the method, as the author states, is a valuable adjunct to biopsy. However, it should be emphasized that because of a reported incidence of "false positives" that may run as high as 2 per cent in the hands of even the most experienced observers, the necessity of obtaining a positive biopsy is obvious and essential before actual treatment for cancer is warranted on the basis of a positive smear. In other words, a positive smear and a negative biopsy should not be considered as presumptive evidence of cancer, even *in situ*. Neither can we dissociate cervical biopsy from endometrial curettage as a practical consideration in the early diagnosis of uterine cancer, whatever its suspected source, and certainly not when we are attempting to "prove" a positive smear to be correct. We have found the circular biopsy more effective than multiple ones.

In a screening study of 5,622 new patients, of whom 3,499 were subsequently examined periodically, a total of 9,121 cytology examinations were made. The results were: 3 positive, 21 suspicious, 50 doubtful, and 9,047 negative. Of the three positives, one patient had the cervix amputated and radium applied seven months previously for carcinoma; in the second, biopsy three months later revealed cervical cancer, and in the third, hysterectomy a month later revealed cervical leucoplakia.

Seven patients had known uterine cancer. Although the smear was positive in six of the seven cases of cancer thus far discovered, six of these patients presented a history together with findings on examination that indicated the need for biopsy and curettage. There was one striking case in which the smears were positive, although the initial examination and subsequent single biopsy were negative. However, subsequent multiple biopsies did reveal cancer. We have also had six patients in whom the smear attracted attention to an unsuspected cancer.

The value of the cytology smear as a screening procedure for "selected cases" will usually be in inverse proportion to a meticulous pelvic examination for which there can never be a real substitute. The experienced clinician uncovers salient points in the history or detects lesions on thorough examination that immediately demand biopsy and/or curettage which a less experienced person may miss or ignore by simply taking a smear. Since the latter may result in a "false negative" in 10 to 30 per cent of cases—and this is the crux of the situation—it is obviously dangerous to give advice or depend upon smears primarily before deciding whether or not a biopsy and/or curettage are indicated. In this sense the smear becomes even more important in those patients whose pelvic examination appears to be grossly normal. The harmful effect of published propaganda on the ease with which smear examinations can detect or rule out cancer, and the mischief causing unwarranted fear on the one hand and a false sense of security on the other have frequently been commented upon by us and by others, and rightly so.

General experience seems to show that as personnel becomes better trained and more experienced, the percentage of "false positives" diminishes. This is especially true when the influence of pelvic inflammatory disease or complications of pregnancy are not apparent, for these are two instances in which difficulty in evaluating smears obtains. On the other hand, as our criteria for positives become more exacting, the tendency to miss more cases may increase. For this reason many cytologists purposely include such categories as "suspicious" or "doubtful" or accept Dr. Papanicolaou's gradation of one to five.

Although in the essayist's hands at the present time a positive smear means to him the presence of cancer, as evidenced by their present figure of  $\frac{1}{2}$  of 1 per cent of "false positives," this was not always so and certainly it is not so in the hands of other workers of experience. Hence, the conclusion that "a positive smear means the presence of cancer" is a dangerous one for the profession at large to rely upon.

2. There have been 8,131 slides and 432 cancers.
3. The false positive error has diminished until in the last year it was only 0.04 per cent. In other words, a positive smear means the presence of cancer.
4. False negative smears continue at about 10 per cent. This figure is due to lack of cells in advanced cases and a lack of exfoliation in others.
5. Smear and biopsy diagnosis are not rival methods but complementary ones.

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### Discussion

DR. LEWIS C. SCHEFFEY, Philadelphia, Pa.—I welcome the opportunity of opening the discussion of Dr. Meigs' presentation, in which he has been so ably assisted by Mrs. Graham. I know that all of us respect and admire the correctness of his observations and the enthusiasm with which he and his group have always pursued their objectives.

We, in Philadelphia, have had an exceptional opportunity, I feel, to evaluate cytologic methods in the diagnosis of uterine cancer, not only in our own institution but in the city at large, because of the cytologic work that we have done for the numerous Health Maintenance-Cancer Detection Clinics supported by the Donner Foundation in cooperation with the Philadelphia County Medical Society. The Division of Cytology of the Department of Obstetrics and Gynecology at Jefferson Medical College and Hospital is under the direction of Dr. A. E. Rakoff, Assistant Professor in the department and Director of the Endocrine Laboratory of the Institution. His accomplishments are well known to most of you. Miss Dorothy Meyers, our associate and head technician, is an invaluable co-worker. What I am able to present is in a large part due to the conscientious labor of these colleagues.

If a single site is to be used to obtain vaginal smears, then the posterior fornix of the vagina is the best source. However, we prefer to collect smears also from the endocervix, the squamocolumnar junction, and directly from any demonstrable lesion, using both pipette and wooden scraper. We have noted instances in which cervical smears were positive when the vaginal smears were negative.

By taking multiple smears and by obtaining such factual data as age, character of menstrual cycle, any recent hormonal therapy, and clinical features noted, we were able to increase the percentage of "correct positives" from 70 to 82.4 per cent in two comparative group studies of 500 patients each, even though the percentage of "false positives" rose from 1.6 per cent to 2.6 per cent as compared with the essayist's Table II. "False negatives" dropped from 30 to 17.6 per cent.

Between 1943 and 1949 we have studied smears from approximately 14,000 patients, of whom about 8,000 were patients in the wards, outpatient clinics, and private rooms

While Dr. Meigs' paper concerned itself primarily with the Papanicolaou technique for discovering carcinoma, he did not confine his remarks to the foregoing. I wish to direct my comments to that part of Dr. Meigs' paper not directly concerned with the Papanicolaou technique. First, I would like to object to the inclusion of these noninvasive carcinomatoid changes, generally called carcinoma in situ, under the general category of carcinoma. I think this represents loose thinking. It is getting us into an untold amount of avoidable trouble and such confusion that some teachers of obstetrics and gynecology are classifying carcinoma in situ as bona fide invasive carcinoma and they are treating them as carcinoma problems rather than problems that require further study. It is also a great mistake, I believe, to speak about carcinoma in situ in a patient who has an established, bona fide carcinoma. Obviously, many carcinomas have an area somewhere at the periphery of the tumor where there is a collateral noninvasive carcinomatoid change. The issue here then is not carcinoma in situ, but a bona fide cancer, and the two should not be confused if clarification is to come to this matter. The significance of these collateral noninvasive cancerlike areas at the periphery of some cancers is not understood. It also has not been proved that a noninvasive (*sui generis*) carcinomatoid change eventually develops into cancer, although the theory is alluring and may possibly be correct. However, that does not now justify a prophetic approach to the problem. I do not think we are justified, therefore, in treating a patient with carcinoma in situ by radical hysterectomy or a modification of the Wertheim operation merely as a precautionary procedure. If a patient has a positive Papanicolaou smear, has no area on the cervix that is suspicious, and if passage of a uterine sound into the cervical canal does not reveal suspicion of friable tissue or unusual bleeding which would indicate the propriety of gentle curettage, or if a previous biopsy has shown only a noninvasive carcinomatoid change, then I believe a conical enucleation of the cervix is indicated. We then have the canal which can be cut into numerous blocks and sectioned. If such a study fails to reveal bona fide carcinoma and if the carcinoma in situ does not extend beyond the longitudinal limits of the sections, that patient, in my experience, requires no further treatment. Still, we have all had experiences where such a clean-cut decision could not be made. The choice of procedure then becomes a matter of individual judgment.

MRS. RUTH GRAHAM, Portland, Ore. (by invitation).—I would like to leave one thought in your minds. In spite of all the lay publicity throughout the past few years, a good many of you who recognize early carcinoma of the cervix are still seeing cases in the late stages. I am sure you have all had the experience of wishing you had seen the patient six months earlier. I think perhaps we will have trained personnel in the future in central laboratories where general practitioners can send the smears they take from the posterior fornix, and if they are positive, perhaps you will see these patients earlier. It is not an office procedure; it is a procedure that takes a good deal of time and experience so it should be set up in hospitals or centers where there is well-trained personnel.

I would like to say that I think you should not ignore this test because no one can afford to disregard any method which may find early carcinomas of the cervix. When the cure rate of carcinoma of the cervix is at its present low figure, any means we can use to improve this low cure rate should be used.

DR. MEIGS (Closing).—We feel that on the whole we know very little about carcinoma in situ. We have done conization operations to cure it and we now recognize our error. We feel that some of these lesions do proceed on into invasive carcinoma. I believe that if a patient has carcinoma in situ, which I feel reasonably sure is carcinoma in situ, I would prefer to take the uterus out rather than take a chance on conization.

Finally, the authors come to the same conclusion that we have constantly been advocating: that the vaginal smear is not a substitute for biopsy as a diagnostic procedure, but rather that it is a complementary method.

DR. WILLIAM J. DIECKMANN, Chicago, Ill.—I have always believed that, if a proper history is taken and a bimanual and speculum examination made by a competent gynecologist, that he could then assure the patient as to whether or not she had carcinoma or that further procedures were required. Dr. Meigs is a competent gynecologist and he states that he detects an additional 1 per cent of cervical and corpus cancers by the Papanicolaou smear in patients who present no other evidence. In view of his findings, as well as those of other competent gynecologists, I believe some form of screening for uterine cancer is indicated.

I wish to call the attention of the Society to a chemical test for excluding 80 per cent of the patients as not having carcinoma of the cervix. Any technician with some chemical training can learn how to perform the test within a day. Dr. Lester Odell on our service has found that if the beta-glucuronidase value of the vaginal fluid is less than 300  $\mu$ g, he can exclude all of the cases as not having carcinoma of the cervix and possibly the same for the corpus. Eighteen per cent of the fluids examined from various gynecologic conditions were false positives so far as we can determine. The test is apparently more specific if a tiny piece (50 mg.) of the cervix is examined.

We hope that the test may be used more generally in order that its exact value can be determined within one or two years. If the test proves reliable it will not only serve as an excellent screening method but will enable the doctor to establish the presence or absence of carcinoma of the cervix by a tiny office biopsy. Thus the number of hospital admissions for cervical biopsy, with its high cost, will be decreased.

The chemical analysis of cervical tissue, especially in the carcinoma in situ cases, may enable us to decide definitely whether this lesion is carcinoma or not.

Dr. Friedman, one of our residents, has been using ultraviolet light and fluorescent stains for detecting the malignant cells in the vaginal smears. He has found certain stains which are picked up by the malignant cells. The field is black and the malignant cells fluoresce brightly. Cellular detail is more distinct.

I do not believe that a hysterectomy or irradiation therapy should be carried out because the woman has an abnormal smear by the Papanicolaou technique or by any other method until more information is available.

DR. JOHN I. BREWER, Chicago, Ill.—We were slow in taking up in our service the vaginal smear procedure. We now use it and our experience has convinced us that it is of value. I would like to discuss one case.

The patient, aged 30 years, had had no symptoms. In taking a routine vaginal smear a positive test was obtained. Four biopsies were taken from the cervix and all four were negative. Because of the positive smear, however, we continued our search. Turning the paraffin block over and sectioning the other side revealed carcinoma in one. Since we call it carcinoma we believe it should be treated as carcinoma, so we irradiated the cervix after doing a biopsy by a modified Sturmdorf amputation. The tissue was studied by serial sections. No invasion was present. One area showed carcinoma within the subepithelial layer; another which was completely separate in serial section showed abnormal epithelium and abnormal mitotic figures. In still another portion there were malignant cells and complete disorientation. Another region separate as demonstrated by serial section showed large cells with multiple huge nuclei and clumping of the chromatin. The last area in serial section was not in the edge of the malignant region but contiguous to it.

I believe the smear procedure is a good diagnostic aid, but we do not treat a patient on the basis of smear alone. A biopsy is always studied.

DR. KARL MARTZLOFF, Portland, Ore.—I would like to ask Dr. Meigs whether a sound was passed into the cervical canal of those patients with unsuspected carcinoma to see if the sounding would produce an abnormal amount of bleeding.

As regards the cervix, the purpose of periodic examinations is coming to mean not only the detection of very early clinical cancer, but also the discovery of preinvasive stages which in an indeterminate proportion of cases are at some unpredictable time followed by the invasion which in former years was looked upon as the *sine qua non* in the diagnosis of malignancy. The still comparatively meager material available in all the laboratories of the world will not for the present permit expungement of the adjectives "indeterminate" and "unpredictable" from the above statement. It is not surprising, therefore, that there is as yet no crystallization of opinion as to the best plan of management of cases in a preinvasive stage when, regardless of future potentialities, they do not constitute a serious immediate menace to the patient's life.

Moreover, it already seems clear that the diagnosis of preinvasive or intraepithelial carcinoma must be made with great circumspection and only after painstaking and often repeated biopsy and meticulous microscopic studies, as has been, most recently and on the largest scale, shown by Galvin and TeLinde.<sup>1</sup> In fifty-five of seventy-five cases in which the initial biopsy showed intraepithelial carcinoma, further study revealed definite evidence of invasiveness. The simple local excision which should cure every case of genuinely preinvasive character would fall far short of requirements in cases of this type.

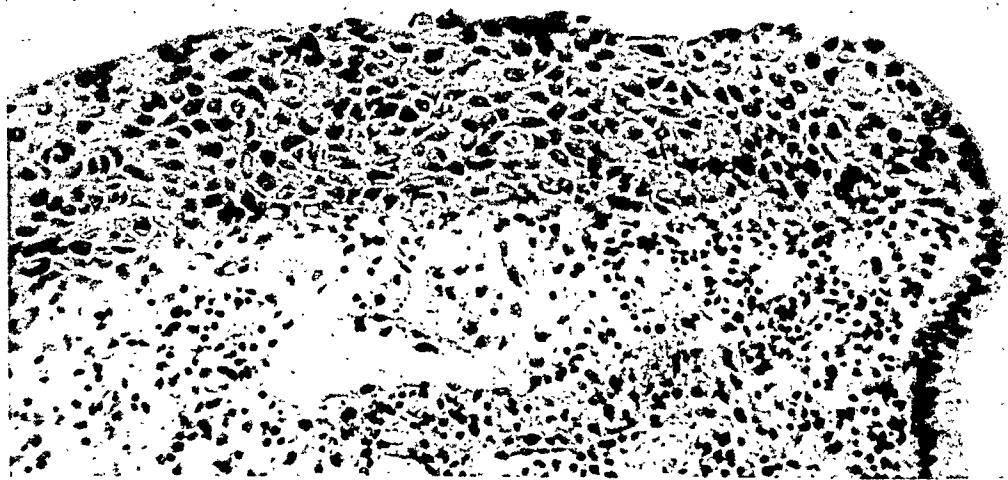


Fig. 1.—Marked epithelial overactivity in cervix of patient twelve weeks pregnant. Following miscarriage at sixteen weeks, repeated biopsies at six weeks, six months and eighteen months post partum showed complete absence of epithelial hyperactivity. (Courtesy of Drs. Louis M. Hellman and J. H. Epperson, Department of Obstetrics, Johns Hopkins Hospital.)

Vaginal cytology cannot differentiate between preinvasive and invasive lesions, and a heavy responsibility is thus placed upon the pathologist. Small wonder that some have decided that the safest procedure is to treat cases of intraepithelial cancer as cases of genuine cancer, with either radical panhysterectomy or radiotherapy. Whether the panhysterectomy is to be of the

## WHAT CONSTITUTES AN ADEQUATE CANCER DETECTION EXAMINATION OF THE CERVIX?

With Comments on the Supplementary Value of Surface Biopsy\*

EMIL NOVAK, M.D., BALTIMORE, MD.

THE most important measure which can be taken by a woman anxious to protect herself from cancer is a competent gynecological examination at periodic intervals, preferably no longer than six months. This statement will seem trite enough, since it has been accepted and publicized by all who are actively interested in cancer educational campaigns, including the American Cancer Society. The developments of recent years have raised the question of what constitutes an adequate examination of the woman who is intelligent enough to present herself for this purpose.

Is it sufficient to secure a history and to make a thorough gynecological examination of the traditional type, including careful inspection and palpation of the abdomen and breasts, examination of the external genitals, careful bimanual palpation of the internal genitals, and especially a meticulous inspection of the cervix in the best possible light? If this is not considered adequate, I believe that most practicing gynecologists have been and most of them still are derelict in their full duty to the patient who presents herself for examination. Such an examination will reveal the presence of a tumor in any of the pelvic organs or in the breast, unless it is so small as to be both impalpable and invisible. As a matter of fact this simple type of examination constitutes pretty much our whole armamentarium in the detection of such common tumors as cancer of the ovaries and cancer of the breast, to mention only the malignant forms.

But in the case of the cervix, with which this symposium deals, is it not true that even a normal-appearing cervix may somewhere in its extent contain a small, invisible, impalpable and symptomless focus of preinvasive carcinoma, which at some unpredictable time in the future may embark on the invasive career of real clinical cancer? And is it not true that even very early invasive lesions have at times been found in such grossly normal cervixes, and with no clinical symptoms? No one will deny these possibilities any more than one can deny that in the entirely normal-feeling breast a hidden group of cells may have already committed themselves to a cancer career. But the analogy with the breast is not complete or sound, since the cervix, unlike the breast, is to all intents and purposes an external surface accessible to more intensive investigation than is possible for the breasts.

\*Presented at the Seventy-Second Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 16, 1949.



Similar divergences of viewpoint are seen in the interpretation of gland invasion, which some appear to accept as definite evidence of invasiveness. However, if in the common lesion of epidermidization, a perfectly benign squamous epithelium can creep along the framework of glands far beneath the surface, certainly an intraepithelial carcinoma can do the same thing. Again, it is not always easy to draw conclusions on this point even on the basis of many sections (Fig. 3).

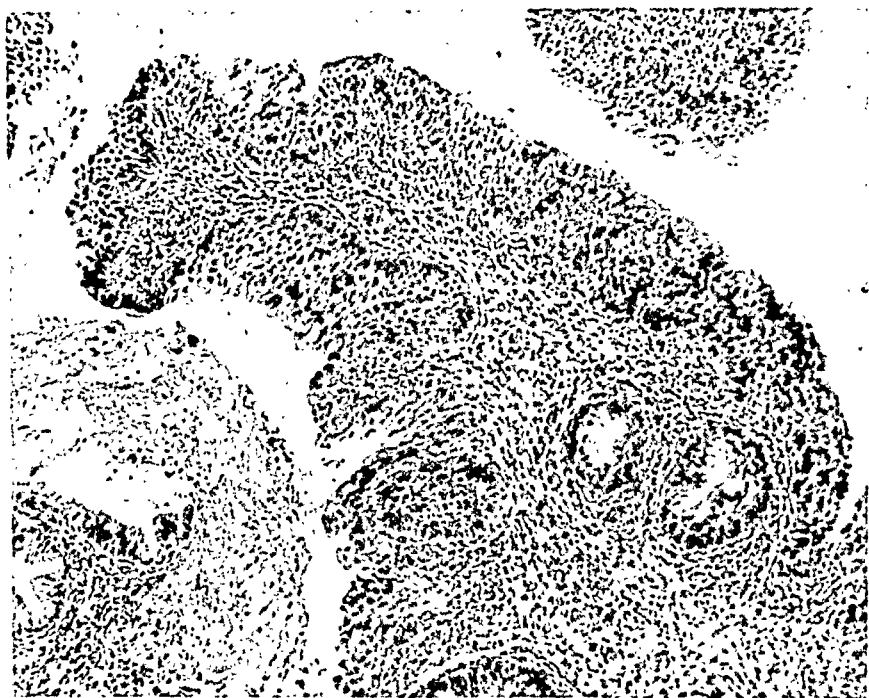


Fig. 3.—Intraepithelial carcinoma showing extension to glands.

If one can actually demonstrate a break-through of the basement membrane, with free penetration of the cancer cells, and, of course, if these can be demonstrated in small lymphatics immediately below the epithelium or in the larger ones well below the surface, there will be no difference of opinion among pathologists as to the invasiveness of the lesion (Figs. 4 and 5). But one would hesitate to say that this should be the sole criterion, and I have heard expert pathologists, like Meyer, say that in the occasional case only a sort of intuition or hunch based on long experience with such lesions must be the basis of a pathological opinion. This does not seem very scientific or helpful to the average pathologist who is called upon to make such diagnoses, but it, at any rate, serves to emphasize this particular point of confusion.

Finally, there has been much discussion of "basal hyperactivity" of varying degree as a possible evidence of epithelial unrest which, to resort to what can be considered either an absurdity or a redundancy, could be called a precursor of the precursory or intraepithelial stages of cancer. Here the fog is even thicker. Some, like Meyer, believe that inflammation is usually responsible for such pictures, while others suggest the hormonal influence which

so-called modified Wertheim type or whether it is to include pelvic gland excision need not be discussed here, as the answer to this question depends on the attitude of the individual gynecologist to the same question as regards Stage I cases in general.

To add to the existing confusion in the evaluation of preinvasive lesions, it now appears that exactly similar pictures are at times encountered in the cervixes of pregnant women (Fig. 1). The role of the pregnancy hormones in producing such cancerlike pictures is indicated by the fact that in at least some cases these lesions appear to regress spontaneously after delivery. Does this mean that preinvasive cancer may at least in some cases be a reversible process? I do not believe that this question can as yet be answered with finality, and we shall probably have to grope our way along until further study clarifies the problem.

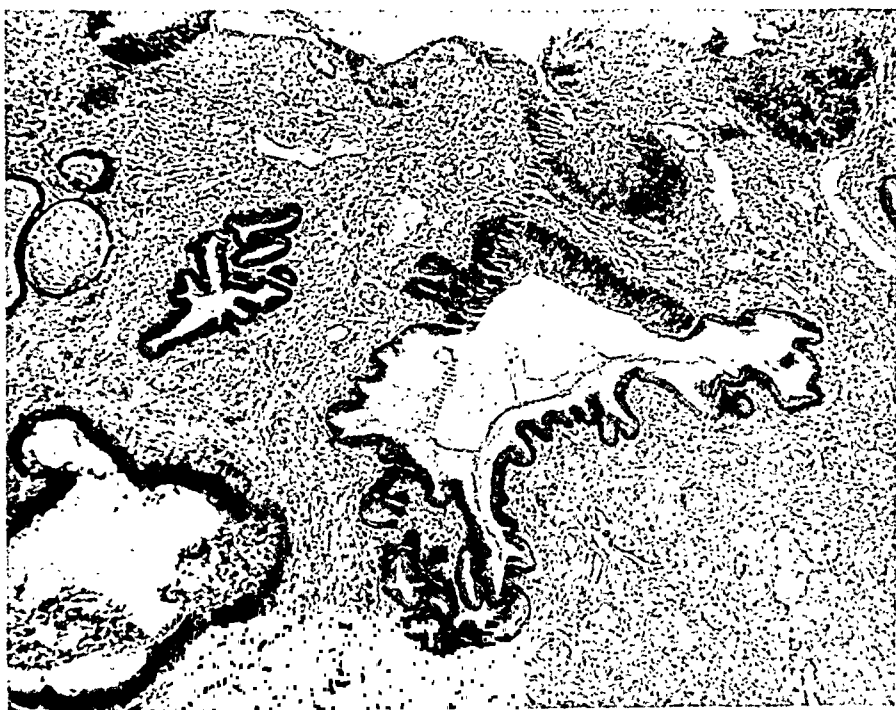


Fig. 2.—Basal budding of intraepithelial lesion, with extension along glands. This is not in itself evidence of invasiveness, although frank cancer of course does often invade or destroy glands.

Another field of confusion in the interpretation of early and precursory lesions pertains to the varying criteria as to what constitutes invasiveness. The buds which project from the under-surface of a cancerous type of epithelium are by some, if one may judge from published photomicrographs, accepted as evidence of invasiveness, even though a sharp and intact basement membrane is seen. Others feel that such pictures are produced by simple buckling of the overactive and crowded basal layers, and do not in themselves justify the diagnosis of early invasiveness, while the ever-present microscopic hazard of misinterpreting tangential sections is always with us, even when many sections are studied (Fig. 2).

brings about varying degrees of basal activity at different cyclical phases, as I shall later discuss.

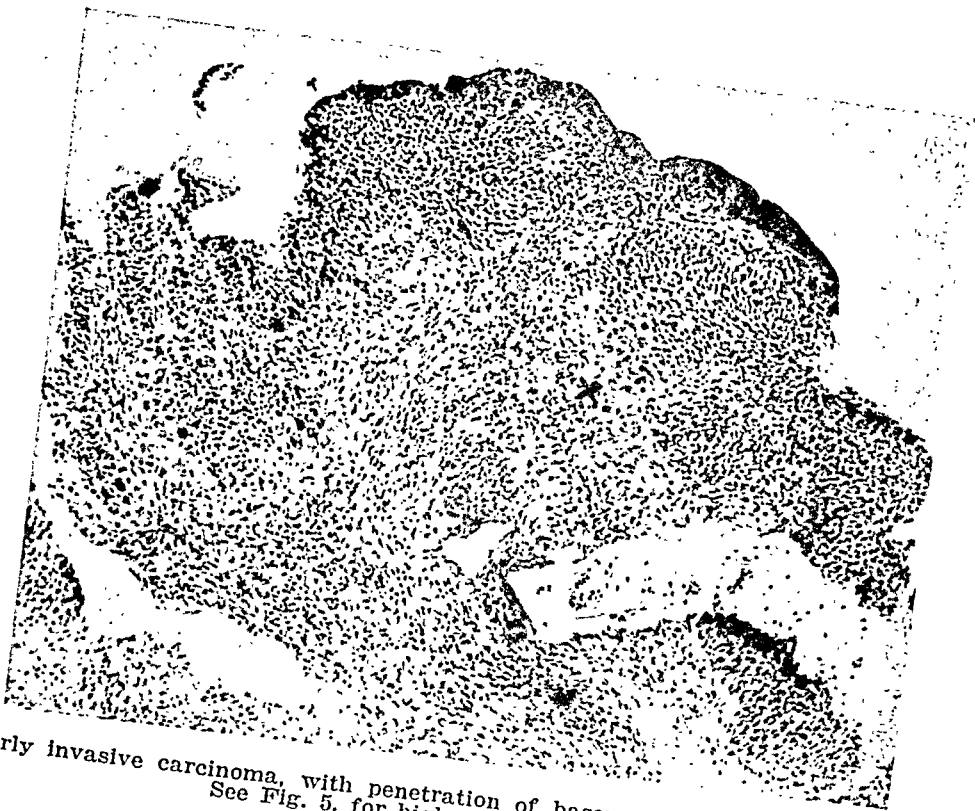
I have felt justified in making this pathological excursion, since it lies at the core of the discussion as to just how far the search for such lesions should influence the scope of the periodic examinations for which women are applying in increasing numbers.

Before discussing the methods available in the search for very early and precursory cancer, it may be emphasized that lesions of this type are highly favorable for treatment, and that preinvasive lesions may remain highly favorable for many years, and often will never become clinically cancerous. Perhaps this will comfort those clinicians who, in their examinations of women who present no such symptoms as abnormal bleeding or discharge, and who have grossly normal cervixes, feel justified in assuring such patients that there is no cause for apprehension. This, I believe, has been the practice of all of us until the past few years, and I do not think it requires any smugness to feel that this policy has not inflicted any noteworthy hazard on the patient.

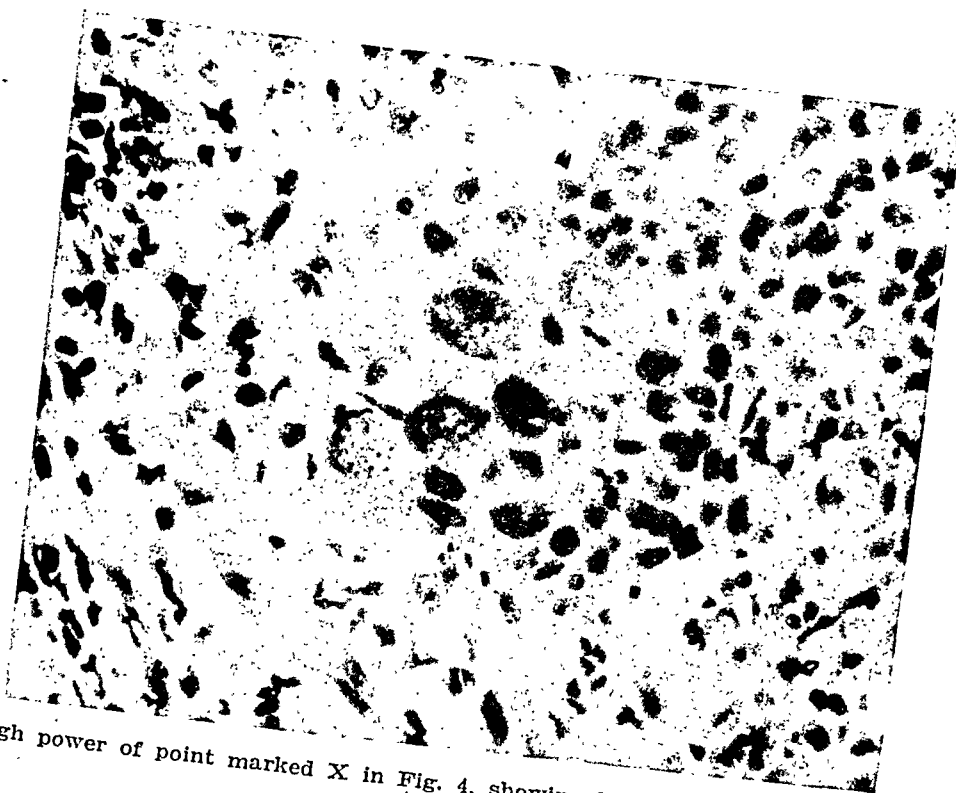
It should be borne in mind that the subclinical and preinvasive lesions which have received so much attention constitute only a very tiny proportion of all cancer cases. If the clinically favorable Stage I cases, embracing those in which the lesion is still limited to the cervix, make up only something like 10 per cent of all cancer cases as they present themselves, then certainly the subclinical group, including the preinvasive, can comprise only a fraction of 1 per cent. And yet they have in recent years been discussed and publicized far more than the clinically early and favorable lesions which are so much more common and which are readily detectable by simple clinical examination, plus biopsy, available to all. Has our cancer campaign gotten a bit out of balance, and are we in danger of losing sight of the woods for the trees?

The relatively uncommon, very early invasive carcinoma of subclinical type, it is true, should be curable in almost all cases by either surgery or radiotherapy, but almost the same statement can be made of the readily detectable lesions of small size, perhaps not over 1 cm. in diameter. As for preinvasive lesions, there is still much confusion as to their significance and proper management. If they are genuinely preinvasive, they should be invariably curable by simple excision, and in a number of reported studies, such as that of Stevenson and Scipiades,<sup>2</sup> cases of this type have remained well for many years, following even simple excision of the lesion.

I am sure that most of us have often, in the course of Manchester operations, amputated cervixes which showed only such gross abnormalities as innocent-appearing erosions, without preliminary biopsy, and that the latter has often been omitted before other simple cervical procedures, such as tracheloplasty, conization, or cauterization. If any one distorts the above statement as anything like a blanket approval for the omission of biopsy before conservative procedures, I shall be highly indignant. No conscientious gynecologist would think of performing such operations without preliminary biopsy if the patient has had even the slightest bleeding, or if the cervical lesion presents such suspicious features as induration, undue granularity, or vascularity.



4.—Early invasive carcinoma, with penetration of basement membrane at several points  
See Fig. 5. for high power of point X.



5.—High power of point marked X in Fig. 4, showing break-through of cancer cells into stroma.

that adequate cytological training requires months of intensive training and constant use of the method. The suggestion made by some that large numbers of technicians be trained to carry on the bulk of this work has thus far excited no noticeable enthusiasm, and it seems doubtful that it will in the foreseeable future.

To subject every patient examined by every gynecologist to either vaginal smear, much less biopsy, might seem ideal, but it is fantastically unrealistic in view of the fact that there is only a handful of really competent vaginal cytologists in the country, and that the larger body of tissue pathologists, something like 1,500, could not possibly examine more than a fraction of the biopsy material with which their laboratories would be swamped. These comments apply to practice in the consulting rooms of gynecologists and general practitioners, and not to cancer detection clinics or out-patient clinics with sufficient laboratory facilities and personnel to do not only routine vaginal smears, but also routine biopsies. It will thus be seen that I am trying to draw some sort of a line between what is practicable in private practice without risk of overlooking lesions in a still very favorable stage, and what should be done in cancer detection clinics which are properly equipped to study this clinico-pathological research problem.

The consulting rooms of a practicing gynecologist are not, as a rule, ideally suited for scientific investigations which require extensive and sometimes tedious laboratory study, but the out-patient departments of well-conducted hospitals, especially those of the larger teaching clinics, are equipped for such purposes. The same statement can be made as regards many of the now numerous cancer detection clinics throughout the nation. I submit that it is in such clinics that a concerted effort should be made to explore fully the potentialities of such screening methods as vaginal cytology. The soundest and most experienced students of this diagnostic procedure seem to have reached general agreement that it has no decisive diagnostic value, but that it is of great value as a screening test. Let them explore its possibilities to the utmost, and let their workshop be those clinics with personnel and equipment adequate for the purpose. There are some who have been wrongfully suspected of a reactionary attitude in so far as vaginal smear diagnosis is concerned, because they still feel uncertain about the future of the method, because they believe it possible that its value has been rather disproportionately accented and publicized, that it is being employed and unauthoritatively evaluated by some who must be considered to be inadequately trained in this not so simple procedure, and that they are fearful that too much concentration on this method will result in a neglect of the more decisive, tried and true method of biopsy in the diagnosis of cervical cancer.

It should not be forgotten that many of the results reported in the literature of positive smear findings in cervical cancer have included preponderating numbers of cases in which the smear was not at all essential for diagnosis, which in some could have been made with reasonable accuracy by simple inspection, and in others with great accuracy by biopsy. The smear technique

But if a normal-appearing cervix can harbor an early invasive carcinoma, certainly the same is true of the cervix with grossly mild pathological features, although reports of unfortunate postoperative developments due to the omission of biopsies in such cases are rare. This may be partly explained by the fact that tiny preclinical malignant foci may be actually cured by limited excision or destroyed by the cautery.

In any event, it must confuse many gynecologists to decide how far they can and should apply in their daily practice, and especially in the periodic examination of ostensibly normal women, the newer techniques which will unquestionably help to unearth an occasional subclinical lesion of either intra-epithelial or invasive type. I do not know how many would go as far as Frank, who, in a very recent paper,<sup>3</sup> speaks of "the somewhat hysterical over-anxiety to ferret out cervical cancer in situ or often only in prospect," and deplors the picture of "women racked by unjustified fears, anxieties, and premonitions of disaster caused by the witch-hunter attitude of the professional cancer tracker." He also quotes Julius Heyman, the director of the well-known Radiumhemmet in Stockholm for something like thirty-three years, as stating that "a carcinoma has never developed in a patient in whom we failed to diagnose the cancerous lesion on clinical examination or on biopsy. There seems to me thus to be some slight discrepancy between the experience of the cytologist and the clinician."

When men of such mature experience and high standing express such an attitude, the average practicing gynecologist may be left confused. Is he or is he not culpable if he does not make routine use of vaginal smears and/or biopsy in the periodic examination of ostensibly normal women with ostensibly normal cervixes? He is fully aware that in such cases an occasional subclinical lesion might thus be revealed by methods which too often are not available to him, or which are simply not feasible in the routine of his daily work. But the application of new knowledge and new methods to conditions of actual practice must include considerations of realism and practicability, and it is a discussion of this point which furnishes the incentive for this paper.

Various authors have called attention to the utter impracticability of a general adoption of the vaginal smear method because of the paucity of qualified cytologists. In an excellent paper Foote and Li<sup>5</sup> estimate the incidence of cervical carcinoma in women over 35 years of age as 1 in 1,500, so that, since at least two slides should be studied and an average minimum of ten minutes is required for each, at least 500 hours of microscopic study is required to reveal one carcinoma. Is it wise, therefore, to incite among women a widespread demand for a method which cannot be adequately supplied at the present time? A course of a few weeks' instruction does not qualify one as a reliable vaginal cytologist. In a recent paper by Fremont-Smith, Graham, and Meigs,<sup>6</sup> themselves ardent champions of the method, the statement is made that "reliance on a diagnosis, for or against cancer, submitted by an inexperienced cytologist constitutes malpractice as surely as does the performance of a major operation by an inadequately equipped surgeon." They also state

been frequent emphasis on various degrees of so-called basal cell hyperactivity. The more moderate degrees of this hyperactivity, it seemed to me, were possibly to be explained on a hormonal, cyclical basis, rather than being indicative of precancerous epithelial unrest. There has been almost no study of the cyclical changes in the stratified squamous epithelium of the pars vaginalis, although the studies of Sjövall have given us considerable knowledge of the histological cycle in the endocervical mucosa. While it seemed reasonable to believe that the hormonal changes in the cervical squamous epithelium would be similar to those in the vaginal mucosa, it was thought worth while to study the problem directly. Biopsy seemed to offer definite advantages over smears as a means of furnishing a comprehensive picture of the changes. It was soon found that the changes are not uniform at all parts of the same cervix, so that surface biopsy, which consists of scraping away most of the squamous epithelium surrounding the canal, was resorted to. We were pleasantly surprised to obtain long strips of mucosa, and the comprehensive picture thus obtained naturally suggested the value of the technique in the search for early or precursory cancer lesions.

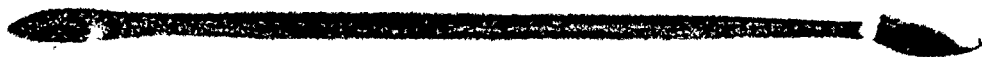


Fig. 6.—Sharp-edged, long-handled, double spoon used for surface biopsy, though ordinary scalpel is often satisfactory.

The instrument we have employed is a scalpel or a long, sharp two-edged spoon (Fig. 6). Cervices differ widely in their size, configuration, and in the degree of patency of the canal, so that sometimes the scalpel and sometimes the spoon is used. The latter, incidentally, is double, with a smaller spoon at one end of the long handle, and a larger one at the other, making easier adaptation to cervixes and cervical canals of different sizes. I feel sure that some one more inventive than I can devise something even better, and we have experimented with various other appliances, but so far the scalpel and spoon have seemed most satisfactory. The entire circumference of the canal, or if this is everted, the junction of the squamous- and cylindric-celled zones, is sharply scraped, and also the endocervix just above the os. The tiny fragments are washed off the instrument in a large tube of formalin or alcohol-ether. They are not stained as a film, but the fragments are centrifugalized and then run through the ordinary paraffin technique, with hematoxylin-eosin staining. Figs. 7 and 8 give an idea as to the long strips of epithelium often obtained. Sometimes they yield practically all the circumferential epithelium, in others they are more fragmentary and less complete. Only a slight oozing surface is left, which epithelizes within a few days.

The procedure has been done as a routine in all vaginal operations during the past year or more, numbering something like 300 cases. The histological

in such cases was done as a supplementary method, for the laudable purpose of familiarizing the examiner with the appearance of exfoliated cancer cells, but this fact should be borne in mind in comparing the diagnostic values of cytological study and biopsy. Everyone agrees that cancer is an exfoliative lesion, and that in the grossly unsuspecting cervix the finding of unquestionable cancer cells should be the stimulus to intensive and more decisive diagnostic study. But this is a part of the screening process, and no one will question the applicability of vaginal cytology in this limited but very important field. But in the presence of a clinically suspicious lesion of the cervix, I for one would consider it a far greater dereliction to omit direct biopsy of the lesion than to omit vaginal smear study. I do not think that Warren's<sup>7</sup> estimate of more than 99 per cent of pathologic accuracy in biopsy is at all excessive. It will be admitted that as a screening procedure the vaginal smear offers certain definite advantages over biopsy. The latter is not nearly as simple, and, even if done at various portions of a cervix which presents no target lesion, is likely to be a random procedure, which may still miss a small subclinical cancer focus. Furthermore, it is a more pretentious procedure and in many cases its proper performance calls for a light anesthetic.

It is in cases of this general type especially that I believe that surface biopsy of the cervix is of great value. The method is an old one, having been suggested by Schiller<sup>8</sup> as far back as 1928 and having no doubt been employed before and certainly since then by various gynecologists and with various techniques. Schiller's suggestion met with very little response, probably because of the skepticism of many at that time toward a method which could not be expected to give information as to the invasiveness which many then felt was essential for the diagnosis of cancer. It is not to be confused with the cervical smear advocated by Ayre and others, as this is only an adaptation of the cytological method, the smear being filmed and stained like the ordinary vaginal smear.

More recently Ayre<sup>9</sup> has recommended a species of surface biopsy performed with a so-called cone knife, the procedure being essentially a superficial scalpel conization. A somewhat similar procedure has been employed by Scheffey,<sup>10</sup> and no doubt by others as well. Ayre states that his method is often followed by moderate bleeding, so that it is often followed by electrocauterization. Still others recommend more extensive conization for the purpose of securing tissue for study, although this is a much more pretentious procedure than simple surface biopsy, and does not always yield satisfactory tissue for microscopic examination. Still another variation of surface biopsy has recently been suggested by Gusberg.<sup>11</sup> It is not my purpose to stress the superiority of any one method of surface biopsy over others, but merely to emphasize the general principle of securing for examination as simply as possible as much as possible of the surface mucosa in the area of cancer predilection.

My own interest in surface biopsy as applied to cancer diagnosis was engendered rather indirectly. In the discussion of precursory lesions there has



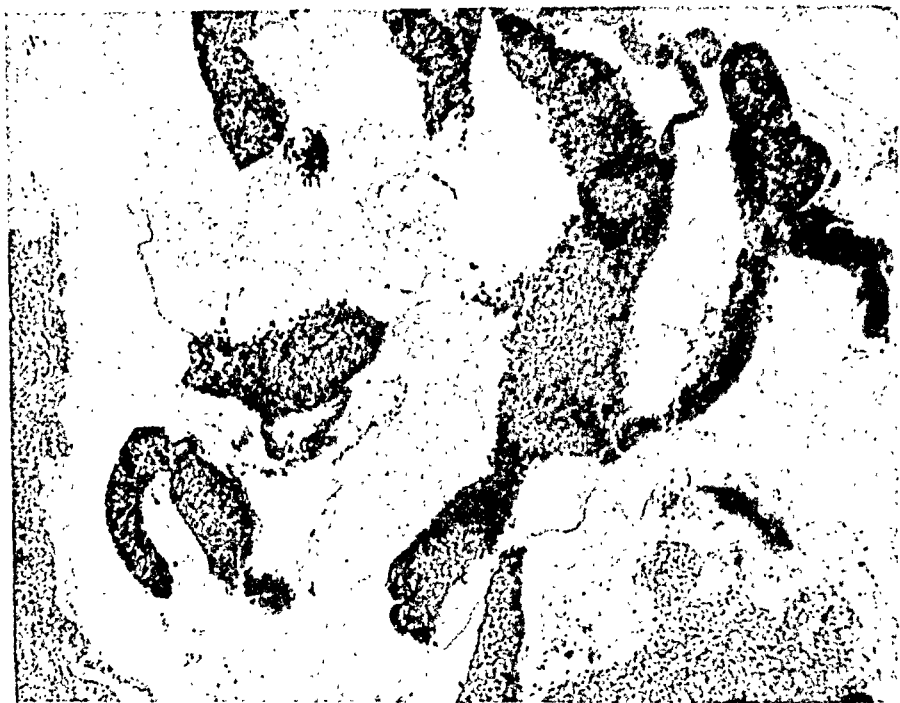


Fig. 9.—Strips of definite cancer epithelium revealed by surface biopsy in a woman 42 years old with an erosion which was slightly vascular at only one point. Punch biopsy of latter negative, but surface biopsy positive. Microscopic examination after radical operation showed very early invasive carcinoma.

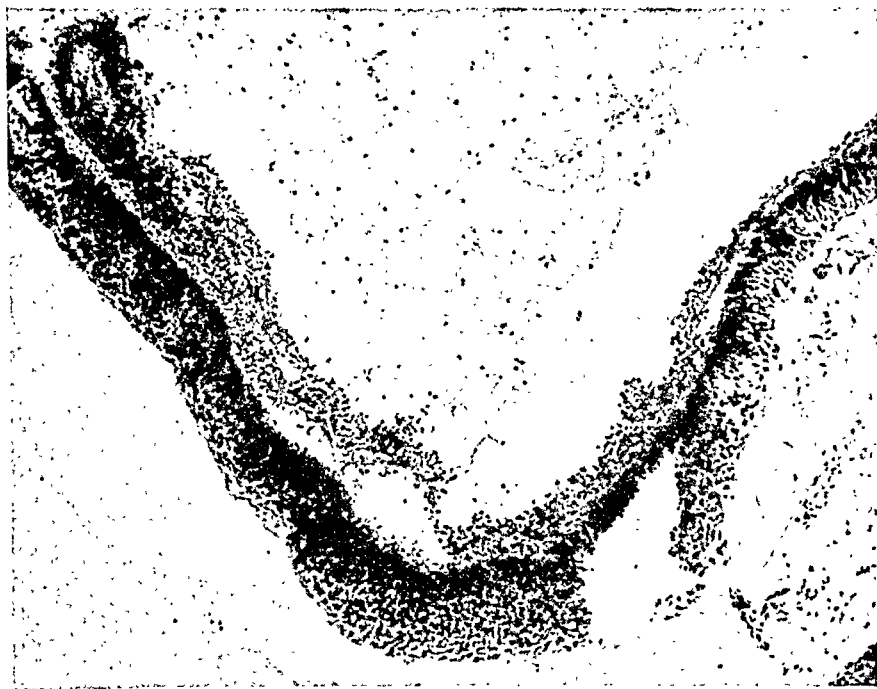


Fig. 10.—Another cancer epithelial strip revealed by surface biopsy. Study of cervix after radical operation showed frank though early invasive carcinoma.

cyclical studies will be reported later in a paper by the author, in collaboration with Dr. A. W. Lyons. That this technique has definitive value in cancer detection may be illustrated by two cases.

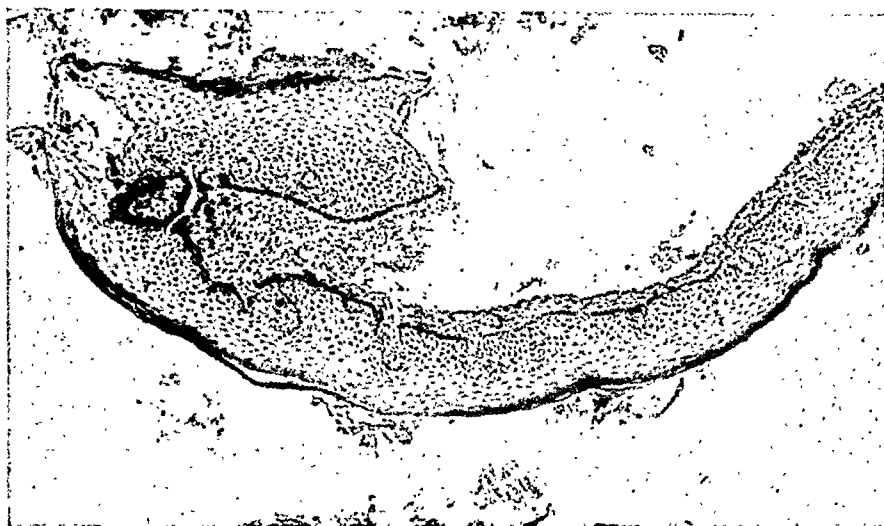


Fig. 7.—Examples of long strips of surface mucosa obtainable by surface biopsy.

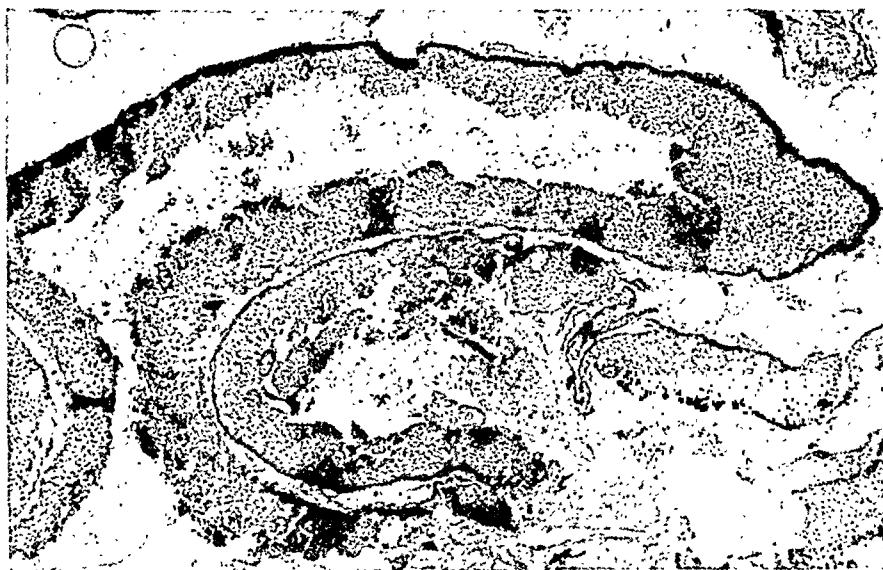


Fig. 8.—Another example of surface strips obtained by surface biopsy.

CASE 1.—F. H., aged 41 years, had slight occasional staining especially on coitus, for several months. Menstruation was somewhat irregular, with cycles of from three to six weeks, but with scantier flow than formerly, lasting two to three days. She had had two full pregnancies, with normal labors, seventeen and thirteen years ago. There were no gross abnormalities of the pelvic organs except that the bilaterally lacerated cervix showed a moderate superficial erosion, but with a small granular area on the right which bled on slight touch. This area was excised with the scalpel, and another biopsy taken at another point. In addition, a surface biopsy was done of the entire cervical circumference. The wedge biopsies microscopically showed only chronic cervicitis, but the cervical scrapings revealed the picture shown in Fig. 9.

this group. The precursory lesions thus far revealed constitute a numerically tiny group, and they appear to be receiving a disproportionate amount of the educational effort. Is our cancer campaign getting a bit out of balance?

The study of lesions believed to be precursory to clinical cancer, especially intraepithelial cancer, is of intense interest, and has great scientific potentiality. On the other hand, it is my opinion that at the present time the lives of many more women will be saved by an intensification of our efforts to increase the proportion of Stage I cases than can be saved by the search for cancer in this preinvasive form.

It is difficult at this time to predict whether or when vaginal cytology will ever become a generally available diagnostic aid. Until such time, which does not appear to be in the very near future, the practicing gynecologist who makes full and conscientious use of universally available methods, including biopsy in the presence of even very small suspicious lesions, will not miss many cancers in a still highly favorable therapeutic stage.

In the screening field, vaginal cytological methods offer definite advantages over biopsy, even of the multiple type, but smears in themselves should not be made the basis for treatment. The limitations of biopsy in women with ostensibly normal cervixes can be largely overcome by some such method of surface biopsy as that described in this paper. It is recommended as a valuable procedure, especially in cases where the cytological smears have been positive.

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### Discussion

DR. NEWELL PHILPOTT, Montreal, Quebec.—We agree that the actual tissue section is the best positive approach to an accurate diagnosis. At the same time Dr. Novak has emphasized the duty of larger teaching centers to investigate the combined approach of a cytological screening with corroboration by a surgical biopsy. We also endorse the statement that cytological diagnosis should be made only by adequately trained personnel and that the technical staff be capable of preparing slides which are diagnosable.

I am in a position of being able to discuss the virtues and disadvantages of the surgical biopsy in comparison to the cytological diagnosis from surface scraping. This is due to the fact that I am frequently called upon to act as referee in a spirited controversy where my Department of Gynecological Pathology does not agree with my Cytological Department.

There are a few points where my opinion varies somewhat with that of Dr. Novak. With reference to cellular changes of the cervix in pregnancy, I should like to state that we

CASE 2.—P. H., aged 48 years, complained of slight postcoital stain on several occasions during the past two months. Menstruation was normal in character and amount, and there was no leucorrhea. There had been one full-term pregnancy with forceps delivery twenty-five years ago, and three early miscarriages, the last fourteen years ago. The cervix was slightly hypertrophic, with a superficial vascular area at the left angle of an otherwise not suspicious-looking erosion. Here again, wedge-excision gave negative microscopic findings, while the surface scraping yielded the lesion shown in Fig. 10.

In addition to these two cases, I have encountered a group of other suspicious lesions in which direct biopsy was positive, but in which the supplementary surface scraping threw additional light on the extent of the lesion. A recent case, for example, showed a long strip of cancerous epithelium adjoining a very small invasive lesion, as determined by punch biopsy. The study of the cervix after the radical operation which was done showed that the lesion was considerably more extensive than might have been surmised from the wedge-excision alone. The supplementary use of surface scraping, therefore, would seem to broaden the scope of biopsy even in the cases in which a definite target lesion is present.

### Summary

The vaginal smear method appears to have established itself as a valuable screening test, but it is not comparable to biopsy as a decisive diagnostic procedure, nor can it distinguish between intraepithelial and invasive cervical cancer.

The possibilities of vaginal and cervical cytology should be fully explored by those fully qualified to do so, and the chief workshop for this purpose should for the present be well-organized and well-equipped clinics. There are still too many pitfalls and limitations to recommend its general adoption among practicing gynecologists.

There must still be uncertainty as to the future role to be played by cytological studies, and some justification for the feeling that their importance has been overaccentuated and overpublicized, for reasons elaborated in this paper.

There is no need for vaginal smear studies in the vast majority of cases of clinical cancer, with existing lesions, either obvious or suspicious, though there can certainly be no criticism of their supplementary employment. The omission of biopsy in such cases is far more culpable than the omission of vaginal smears.

While intraepithelial carcinoma is now commonly accepted as a precursor of invasive cancer of the traditional clinical type, there is still much uncertainty as to the chronological and histological relations between the two. The lack of crystallization of opinions as to the therapy of intraepithelial carcinoma is understandable in view of our still meager knowledge on these points.

Only about 10 per cent of clinical cancers are in the favorable Stage I, so that there is still a tremendous need for the education necessary to enlarge

by the experimental production of such cervical lesions by the oversupply of anterior pituitary and ovarian hormones (see this JOURNAL, Vol. 27, No. 5), and the specific response of the cervical epithelium to hormonal stimulation was duly stressed.

DR. JOHN W. W. EPPERSON, Baltimore, Md. (by invitation).—Studies of the pregnant cervix have been made with a punch biopsy forceps during the past year. No cervical or vaginal smears have been done but it is expected to continue this study by these other methods in the near future. At the present time a total of 290 patients have been biopsied during pregnancy and the puerperium. A total of 780 biopsies have been obtained without an increase in the rate of abortion, stillbirth, or premature labor.

Of the biopsies obtained prenatally, 15 per cent have hyperactivity of the basal layer of the stratified squamous epithelium. Six patients have had a diagnosis of intraepithelial carcinoma of the cervix, which was confirmed by competent pathologists throughout the United States. Of these six patients all were normal in the postpartum period. Two patients were followed eighteen months, two have been followed six months, and one patient was followed five months. All of these patients continue to have normal biopsies. One patient did not return to the dispensary after her first postpartum visit and has not been followed. Of the patients with basal cell hyperactivity during pregnancy, 85 per cent were completely normal in the fourth postpartum week.

DR. NOVAK (Closing).—In his discussion Dr. Philpott alluded to the possible harmfulness of surface biopsy, but I cannot conceive of any element of harm in the procedure. The raw surface left is smoothly epithelized within a few days, and only occasionally is it necessary to touch up an oozing area with the cautery point. It is precisely in the group of cases mentioned by Dr. Philpott, in which the absence of a target lesion makes scalpel or punch biopsy a rather random procedure, that surface biopsy would seem to have its clearest indication. No intelligent person will criticize the use of vaginal smears when these are properly evaluated, and not in themselves made the basis for decisive treatment. But one cannot avoid a feeling of irritation in reading some of the articles in lay publications which do not make clear the limitations of the method, as well as its unavailability to all but a small fraction of the women of the country.

have completed a study in 1,500 cases at different stages of pregnancy. We have found marked secondary hyperplasia which some may term precancer cells, but this should not be confused with the true cancer cell.

In our clinic we place more reliance upon the cervical scraping than upon the vaginal smear. We believe that these scrapings will usually indicate a type of cell change in morphological and staining characteristics which will lead one to suspect or discount the possibility of invasive cancer. Of course, this should be corroborated by surgical biopsy. We think that the so-called intraepithelial lesions can be followed with more safety by means of repeated cytological studies than by the repeat punch biopsies which may be harmful. And, although we are doing ring biopsies of the whole squamocolumnar junction in order to obtain multiple sections, we are not satisfied that this procedure is to be recommended wholeheartedly except for accurate diagnosis.

I should like to ask Dr. Novak if he thinks that preclinical cancer is very rare because a biopsy is taken too infrequently. Since the advent of cytology smears we have had a tremendous increase in incidence. In the last three and a half year period we examined 7,830 cases; 106 of these cases should be classed in the preclinical group of cancer of the cervix; 41 were diagnosed as preinvasive, and all cases had a corroborating pathological diagnosis.

In an article published from Mengert's Clinic by Diddle and collaborators, it states: "Since routine cytology tests were done in the last twenty months almost as many noninvasive carcinomas of the cervix were discovered as were found in the preceding ten years."

Results in our "Well Woman Clinic" show that cervical cancer rarely occurs without some clinical manifestation, but the situation is very different in our general gynecological outpatient clinic. All these patients have symptoms of trouble, and many present what Dr. Novak so well describes as grossly mild pathological features, such as a catarrh or an erosion of the cervix. In this type of patient the cytology smear has proved invaluable. Since routine smears have been the procedure for a two and a half year period, most cases were accurately diagnosed clinically. However, in a total of 4,000 cases of patients who presented themselves, fourteen individuals were examined by competent members of my staff and the patients sent home. They were given instructions for treatment and were told to report at a later date. The cytology report which was presented twenty-four hours later gave positive findings. Nine of these cases were proved to have invasive cancer and the other five were of the intraepithelial type. These were definite "misses" on the part of the clinician.

We are all agreed that cancer can be cured only if it is treated in the early stages. Surely more emphasis should be placed upon the developing of a system to make this early diagnosis possible. The results would be more gratifying and would have less tendency to cause cancer phobia than our present approach of late diagnosis and treatment by spectacular but disappointing means such as pelvectomy, the Wertheim operation, or massive radiation therapy.

An adequate clinical examination is basic. Our recommendation is that cytology be coupled with this initial approach. Cytology is an excellent screen and gives a lead to further search. However, it cannot at present be taken as final or as a basis for active treatment. The surgical biopsy gives a comprehensive picture if taken from the offending area. In so-called preclinical cancer it is usually a difficult task to find this elusive area. In addition, repeat biopsies are traumatizing and may cause spread of an existing cancer.

DR. J. ISFRED HOFBAUER, Cincinnati, Ohio (by invitation).—The morphologic appearance of the manifestations of hyperplasia and metaplasia of both the surface mucosal epithelium and the glandular cervical epithelium with well-defined ingrowths and hyperchromatism during gestation was fully detailed in a paper published in this JOURNAL in 1933 (Vol. 25, No. 6). It was suggested that "the production of solid tongues of proliferating epithelial cells in the cervical mucosa may represent an important link in the chain of causative factors for the later development of malignancy. As an important element in cancer prophylaxis, proper inspection in the postnatal clinic of the cervical tissues and immediate attention to any vascular or granular area seems imperative." The inciting causes of the hyperplasia and metaplasia of the cervical epithelia incident to gestation were determined

published his first description of what he called "beginning carcinoma" of the cervix. He believed that these noninvasive lesions were definitely carcinoma. In 1932, Broders,<sup>5</sup> under whom one of the authors studied (P. A. Y.), introduced the term "carcinoma in situ" which has been used since 1936 in this clinic. The same cervical lesion frequently is described by other terms, such as, "noninvasive potential carcinoma," "Bowen's disease of the cervix," "incipient carcinoma," "preinvasive carcinoma," and "superficial noninvasive intraepithelial carcinoma," or just "intraepithelial carcinoma." For purposes of clarity this histological entity will hereafter be referred to as carcinoma in situ.

Since 1933, numerous papers have been published on the microscopic picture of carcinoma in situ and the minimal criteria necessary for the diagnosis of this preinvasive stage of cervical cancer. On the other hand, there have been very few reported cases that have been followed without treatment which is the only way to determine the exact potentialities of this disease. The work of Pemberton and Smith,<sup>6</sup> who first reported this type of follow-up study in 1929, will be discussed in detail later. Others who have found carcinoma in situ progress to invasive cancer in addition to Smith and Pemberton's<sup>17</sup> four cases are: Schiller,<sup>7</sup> three cases; Stevenson and Seipiades,<sup>8</sup> two cases; Younge,<sup>9</sup> two cases; Knight,<sup>10</sup> two cases; Schmitz and Benjamin,<sup>11</sup> one case; Rubin,<sup>12</sup> one case; Goldberger,<sup>13</sup> one case; Taylor and Guyer,<sup>14</sup> one case; Pund and collaborators,<sup>15</sup> one case; and Te Linde,<sup>16</sup> one case—a total of nineteen cases.

Te Linde's patient died of metastatic carcinoma of the cervix six months after irradiation therapy for carcinoma in situ. A reasonable doubt, therefore, exists in our minds that this case had only carcinoma in situ at the time of her treatment. The same doubt exists for one of Smith and Pemberton's<sup>17</sup> cases. Also one of the cases reported by Younge<sup>9</sup> in 1939 has been excluded because we do not agree now on the diagnosis of the original biopsy specimen.

In this paper two hitherto unreported cases will be cited in which carcinoma in situ progressed to invasive cervical cancer. Thus, at the present time, there are only eighteen such cases in the literature.

### Experience at the Free Hospital for Women

In 1929, Pemberton and Smith<sup>6</sup> of the Free Hospital for Women reported three cases of carcinoma in situ of the cervix among sixteen cases of unsuspected cervical carcinoma. One of the cases was diagnosed incorrectly as benign at the time a trachelorrhaphy was performed. When, however, this patient returned four years later with invasive cervical cancer the slides were re-examined, and the diagnosis of carcinoma in situ was made. This patient upon whom the trachelorrhaphy was performed in 1916, and who died of cancer of the cervix in 1920, is the first case in which carcinoma in situ unwittingly was observed to progress to infiltrating cancer. That same year, 1929, an additional case of carcinoma in situ was discovered in an amputated cervix by Dr. Pemberton. The slides were sent to Drs. Frank B. Mallory and James Ewing. Dr. Mallory wrote: "My opinion on No. 16780 is as follows: More or less dilatation of cervical glands, some of which contain mucus and polymorphonuclear leucocytes; infiltration of the submucosa with many leucocytes and plasma cells and a few eosinophils; extension of the squamous epithelium covering the surface for some distance into some of the glands; marked proliferation of the epithelium; mitoses very numerous. It evidently does not mean malignancy. The unusual feature in your case is the marked proliferation of the

## A STUDY OF 135 CASES OF CARCINOMA IN SITU OF THE CERVIX AT THE FREE HOSPITAL FOR WOMEN\*†

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THE concept that carcinoma in situ of the uterine cervix is a preinvasive stage of cervical cancer has been considered for many years. Definite proof that this concept is valid has yet to be presented. The questions which must be answered to prove the validity of this controversial subject are: 1. Does the disease occur at a regular rate consistent with the incidence of undoubted cancer of the cervix? 2. Is the average age incidence consistently less than that for invasive cancer? 3. Is the disease an irreversible process? The experience with noninvasive carcinoma of the cervix at the Free Hospital for Women for a period of nearly twenty years can answer the first two questions and shed light on the third.

### Review of Literature

In 1912, Schottlaender and Kermauner<sup>1</sup> described the surface coating of malignant epithelium (Fig. 1A) at the periphery of invasive cancer (Fig. 1B). I. C. Rubin,<sup>2</sup> a student of Schottlaender, in 1910, reported three cases of "incipient carcinoma" of the cervix. Rubin's first two cases, as he described and pictured them in drawings from serial sections of the whole cervix, were examples of carcinoma in situ with extension into the cervical glands. A radical hysterectomy was performed on the first case, and the iliac and hypogastric lymph nodes were negative. His third case probably represented "epidermoid hyperplasia" in a prolapsed cervix. Rubin's question, nearly forty years ago, presents the problem as it exists today: "What shall we regard as metaplastic, nonmalignant, epithelial changes, and what shall we regard as typical carcinomatous epithelium, or an atypical epithelium that will sooner or later develop into a full-fledged carcinoma?" Rubin concluded, "The important criteria of malignancy in these early cases lie not so much in the relation of the cell nests to the stroma, the depth or extent of epithelial invasion, or evidence of surrounding inflammatory changes, as in the intrinsic morphology of the epithelial cells."

Cullen,<sup>3</sup> in 1921, published a report of an unsuspected case of early cancer of the cervix which has been considered in the literature as one of the earliest reported cases of carcinoma in situ. From Cullen's description and photomicrographs his case is an early invasive cancer. His paper, however, did much to stimulate interest in finding more cases similar to Rubin's. Seventeen years after Rubin's paper, one of Kermauner's students, Walter Schiller,<sup>4</sup>

\*Aided by a grant from The American Cancer Society (Massachusetts Division).

†Presented at the Seventy-Second Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 16 to 18, 1949.



cases of early cervical cancer. Now early beginning cervical cancer is not true cancer in the clinical sense, so don't you go to work and take out this woman's uterus. All that is needed is a smart dose of radium in the cervical canal. This type of lesion is apt to run well up the canal. I am further pleased at differing with my good friend Mallory." Although the patient's cervix had been amputated, a "smart dose of radium" (3,300 mg. hours) was given, and she was alive and well fifteen years later.

The same slide was shown to seven pathologists at a meeting of the New England Pathological Society in 1938, and six of them thought the case was definitely malignant.

Between 1929 and 1934, three patients, upon whom trachelorrhaphy had been performed three to twelve years previously, returned to the Clinic, or were reported to us from other hospitals as frank cancer of the cervix. These cases, whose original slides were diagnosed incorrectly and later changed to "early cancer" (carcinoma in situ) resulted in the writing of "The Picture of Early Carcinoma of the Uterine Cervix" by Smith and Pemberton<sup>17</sup> in 1934. Four<sup>18</sup> of the sixteen cases reported developed clinical cancer three, four, six, and twelve years later. Six of their sixteen cases are excluded from this series after re-examination for the following reasons: four cases showing definite invasion, one anaplasia, and one with insufficient epithelium for diagnosis. The last patient developed carcinoma twelve years later and although the original cervical biopsy shows a definite carcinoma in situ pattern, the two fragments of surface epithelium are too small to be conclusive.

In 1931, a trachelorrhaphy specimen (Path. No. 18737)<sup>19</sup> was examined by Dr. George Van S. Smith who thought it was suspicious and probably even malignant. In deference to the opinion of other pathologists in similar cases, he committed himself to diagnosis of "chronic cervicitis." This patient's cervix was cauterized in the Out-Patient Department twice during the next two years. In 1934, three years and four months after the trachelorrhaphy, a biopsy showed definite invasive carcinoma. In spite of radium and x-ray therapy at this time, she died of generalized metastases in January, 1939, eight years and three months after the trachelorrhaphy. An autopsy confirmed the diagnosis. At the present time, our opinion of the original slide is that it shows only the minimal criteria to substantiate the diagnosis of carcinoma in situ because there is so little epithelium present. Also, we cannot be certain that it was not an invasive cancer in 1931, but the only tissue we do have shows two small areas of carcinoma in situ.

Having discovered the above case in 1934, shortly after Smith and Pemberton's paper was published that same year, we were convinced more than ever that carcinoma in situ was the early stage of cervical cancer. The experience with these cases was the foundation for our interest and knowledge of this disease.

In 1936, the diagnosis of carcinoma in situ was made on a biopsy specimen (Path. No. 26609). Dr. Frank B. Mallory made the diagnosis of "nonmalignant reparative process"; a second pathologist, Dr. Shields Warren, as "nonmalignant although precancerous"; and three other pathologists (Tracy B. Mallory, George Kenneth Mallory, and Frederic Parker, Jr.) agreed with us. One of those agreeing with us wrote that the slide was so extremely suspicious that he would not dare to report it as nonmalignant. He added that he did not feel a strong enough conviction, however, to be willing to include it in any series of cured cancers of the cervix. Since this patient's cervix was thoroughly cauterized at the time the biopsy was performed, we cannot say from the experimental point of view what would have happened to that

\*One of these cases was reported by Pemberton and Smith in 1929.

epithelium. This may be due to injury by some chemical, for example, iodine, followed by active regeneration. Diagnosis: Chronic cervicitis."

The above quotation is a good objective description of carcinoma in situ by a famous pathologist who insisted upon invasion as one of the criteria for the diagnosis of carcinoma. Also, it is interesting to note that Dr. Mallory did not mention the aberrant location of the mitotic figures and the loss of differentiation, histological features which characterize carcinoma in situ.



Fig. 1.—A, The noninvasive surface epithelium of the portio from a case of clinically evident squamous carcinoma of cervix. The normal portio epithelium is on the left and the malignant, but noninvasive, neoplastic epithelium is on the right. Note hyperchromatism and lack of differentiation. (This "surface coating," at the periphery of definite cancer, was first noted by Schottlaender and Kermauner, S-43-2414.) ( $\times 100$ .)

B, Typical squamous carcinoma from same case as seen in A, S-43-2516. ( $\times 150$ .)

Dr. James Ewing on the same case wrote to Dr. Pemberton: "I am inclined to agree with you that the cervix slides you sent me show beginning carcinoma. It is very early, shows no definite infiltration, but the cell layer is much thickened, and the cells show marked hyperchromatism. They look like cancer cells. Kermauner has described just such superficial, wide-spread

diagnosis, it was decided to follow the patient without treatment because of the clinically benign cervix. In order to relieve our conscience about merely following a patient with noninvasive cancer, we decided to perform this experiment only if another pathologist *disagreed* with our opinion. Dr. Shields Warren examined the slide and gave the diagnosis of "not malignant but precancerous. Follow patient carefully." His opinion was based upon the fact that there was no evidence of invasion. Six and one-half months later a biopsy from the same area again showed carcinoma in situ, and a specimen from the posterior lip showed normal epithelium. The lesion on the right side of the anterior lip of the cervix was described as having slight increased redness of the squamous epithelium and a positive Schiller test. Eleven months following the initial biopsy, a third was taken with a curette showing fragments of carcinoma having broad pegs suggestive of stromal invasion. The cervix was amputated and serial blocks, or "step sections," revealed only a very small invasive squamous carcinoma 5 mm. in greatest diameter *at the site of the original carcinoma in situ* (Fig. 3). The cancer was found in only one block of tissue; the remaining sections showing only anaplasia. The patient had no further treatment, is alive and well, free of disease, and has a negative vaginal smear eleven and one-half years after the first biopsy. In this deliberate experiment, carcinoma in situ developed into a frankly invasive, but symptomless carcinoma in eleven months.

### Material and Methods

Since that experiment ten years ago, a rule has been established in the Clinic to biopsy every eroded, everted, or positive Schiller test cervix, and determine the pathological diagnosis before treating the patient. This routine biopsy practice in the Out-Patient Clinic has rewarded us with fifty-eight (43 per cent) of the cases in this series. Forty-two additional cases were discovered by biopsy at the time of a conservative pelvic operation. Thus, 100 out of the 135 cases in this series were discovered by the routine biopsy practice. The remaining thirty-five were found incidentally following other pelvic surgery, usually hysterectomy as shown in Table I.

TABLE I. ORIGINAL DIAGNOSIS MADE FROM TISSUE OBTAINED

AT THE TIME OF	NO. OF CASES	PER CENT
Routine* clinic biopsy (ambulatory)	58	43.0
Routine biopsy at time of dilation and curettage, repair operation, pelvic laparotomy, or supra-vaginal hysterectomy <sup>4</sup>	41	30.4
Cervix from complete hysterectomy	21	15.6
Cervix from vaginal hysterectomy <sup>1</sup> or amputation <sup>5</sup> as part of repair operation	6	4.4
Trachelorrhaphy	6	4.4
Curettage for miscarriage	2	1.5
NEW PUNCH USED to obtain tissue from normal nulliparous cervix	1	0.7
Total	135	100.0

\*No. 47-4428. After three positive vaginal smears, diagnosis made from endocervical biopsy in office. Dilatation and Curettage and biopsy of cervix negative in operating room. Carcinoma in situ with early invasion at hysterectomy four months after first positive smear. This is the only case in the series in which the vaginal smear led to the diagnosis.

The fifty-eight patients diagnosed in the Out-Patient Department were studied by multiple biopsies over a period averaging forty-eight days before final treatment was performed. Most of these patients were observed by one of the authors (P. A. Y.). In addition to frequent observations and repeated biopsies, colored photographs were taken of many of these cervixes between the first and second positive biopsy as well as after hysterectomy.

lesion had it not been destroyed. Although she is alive and well twelve years later, a recent biopsy shows some degree of anaplasia in her cervical epithelium.

By 1937, in spite of our experience with five patients developing invasive cancer three to twelve years later, very few pathologists at that time agreed with the opinions of Schiller, Broders, Pemberton, and Smith. It seemed necessary, therefore, to follow deliberately an untreated carcinoma in situ to discover whether the process was reversible or not.

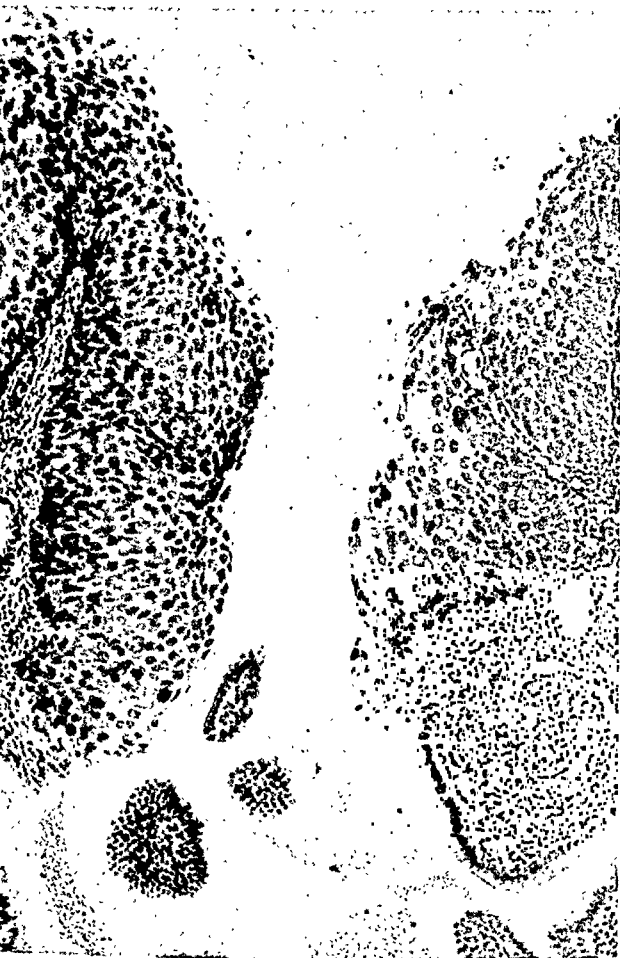


Fig. 2.



Fig. 3.

Fig. 2.—From a case of classic carcinoma in situ of the cervix with glandular involvement leading to invasive squamous carcinoma at the site of the original biopsy twelve months later. (Path. No. 27434) Biopsy taken from "11 o'clock" on anterior lip of cervix. Note lack of surface basal layer, pleomorphism and hyperchromatism of nuclei. The entire basal layer, pleomorphism and hyperchromatism of epithelium has involved or grown into the gland there is no stroma.

Fig. 3.—The same site from which the original biopsy seen in Fig. 2 was taken but twelve months later showing the entire squamous carcinoma measuring approximately 5 mm. in diameter. Note invasive lesion in center, glandular involvement at top and normal surface portio epithelium below on right. This emphasizes the site at which most carcinomas in situ originate in the cervix. (X70.)

On Feb. 5, 1937, a mildly eroded cervix was biopsied in the Out-Patient Department by an intern who was following the routine biopsy practice. The patient's complaints were due to trichomonas vaginitis. The biopsy (Path. No. 27434) showed a typical carcinoma in situ (Fig. 2). In the operating room the anesthetized patient was examined by Dr. George Van S. Smith. It was his opinion since the cervix was normal clinically that no treatment was necessary. Although subsequently he agreed with the pathological

### Incidence

Although the number of cases of carcinoma in situ seen annually in this one clinic has increased tremendously (four in 1937 and twenty-eight in 1947), the rate of occurrence has remained constant. In the Out-Patient Department, since 1930, practically all pathological but benign appearing cervixes have

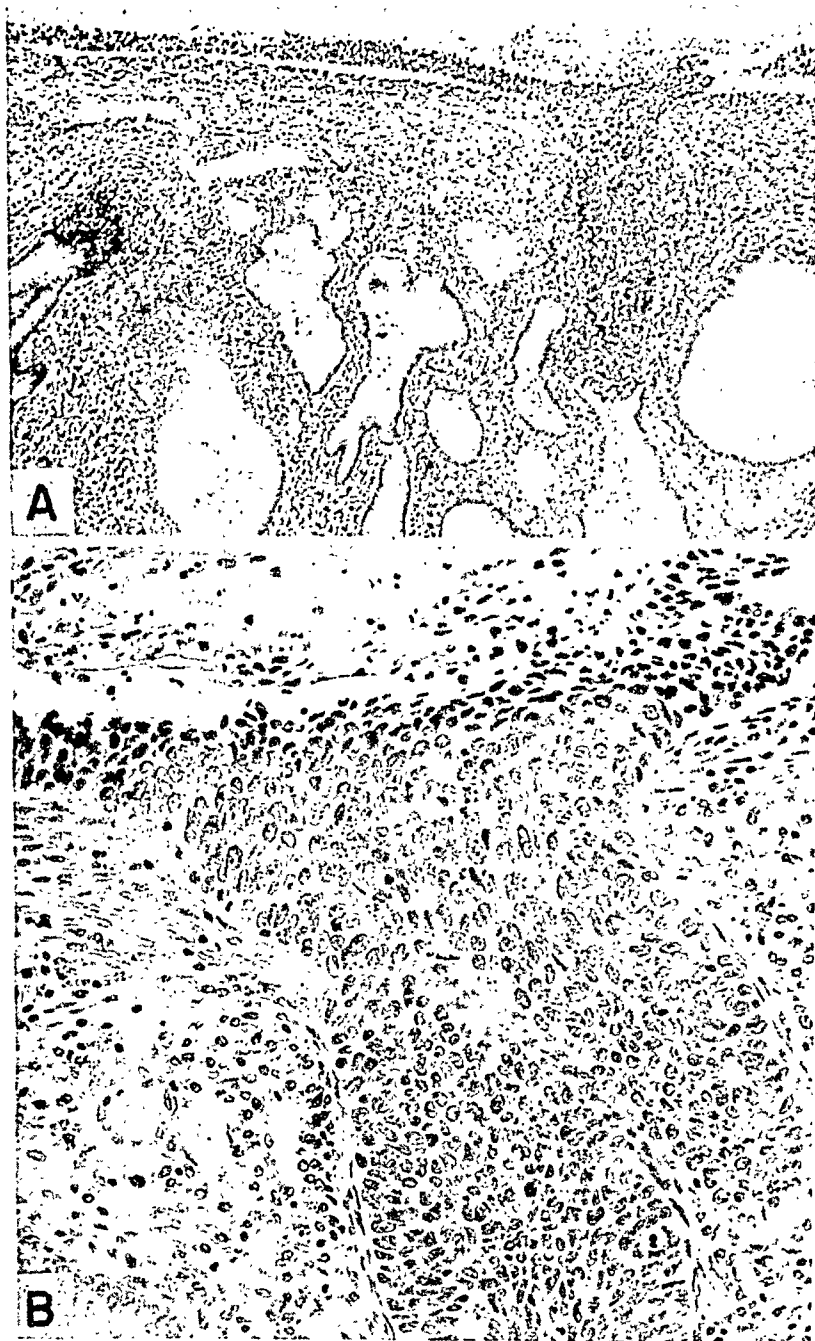


Fig. 4.—From a classic case of carcinoma in situ of the cervix showing glandular involvement. S-47-1705.

A, Low power, orienting view to show neoplasia of surface epithelium with downgrowth of latter into a gland. Note replacement of epithelium in upper half of gland. (This is not considered to be true invasion.) ( $\times 100$ .)

B, High power view of A to show cellular detail of neoplastic surface epithelium involving the neck of a cervical gland. Note lack of differentiation and desquamation of malignant cells from surface. It is significant that the vaginal smear was positive in this case. ( $\times 400$ .)

As stated previously, all pathological cervixes are biopsied routinely, usually at 6 and 12 o'clock at the junction of the erosion and normal-appearing squamous epithelium of the portio vaginalis. Other sites are biopsied according to the dictates of a carefully performed and accurately interpreted Schiller test. This test was performed on twenty-nine of the fifty-eight patients studied preoperatively. In twenty-seven of the twenty-nine patients the Schiller test was positive and was directly responsible for the discovery of an early, usually well-localized, and curable cancer.

In spite of the utter simplicity of the Schiller test, its value is not understood by many physicians because they fail to interpret it correctly. Gram's iodine solution will stain normal squamous epithelium of the cervix and vagina a deep brown but not the columnar or metaplastic epithelium of the cervical canal or erosion. Not realizing this fact, many physicians mistakenly have regarded the "*nonstaining erosion*" as a positive Schiller test. Frequently the *nonstaining* squamous epithelium at the periphery of an erosion is just a narrow band, well localized, and it is overlooked easily as it appears to be part of the erosion after the solution is applied. Only by very accurate observation of this fact is the test of value in selecting the biopsy site. Also it must be understood that a positive Schiller test merely indicates the absence of glycogen in the cytoplasm of squamous epithelial cells and is, therefore, not a diagnostic test. Only the pathologist can say whether the nonstaining epithelium is a leucoplakia, paraleucokeratosis, or a cancer. Approximately 90 to 95 per cent of the positive Schiller tests are due to benign paraleucokeratoses, yet there is no way short of biopsy to distinguish the difference except by submitting the tissue to a well-trained gynecological pathologist.

A square-jawed punch is the most satisfactory instrument for performing a cervical biopsy for two reasons: 1. There is little danger of cutting too deeply causing serious hemorrhage. 2. More important than the occasional embarrassing hemorrhage is the fact that a square-jawed punch obtains a specimen which the personnel of the laboratory can orientate in the paraffin block so that the microscopic sections are cut at right angles to the surface. The most satisfactory punch in our experience is the Yeoman's biopsy forceps, a handmade German product unobtainable since 1940.\*

All of the slides originally diagnosed up to Jan. 1, 1948, as "early cancer of the cervix," "suspicious of cancer," and "definite carcinoma in situ" have been re-examined carefully by all three authors independently. Many such cases were excluded from this series because they no longer meet our criteria for the diagnosis of carcinoma in situ either because they show definite or extensive invasion or merely anaplasia. A few cases, originally diagnosed ten to fifteen years ago, we now interpret as squamous metaplasia or anaplasia of repair. This left 135 cases of definite carcinoma in situ, an example of which is seen in Fig. 4. One hundred fifteen of the cases are typical, meeting all the microscopic criteria for this disease entity, and twenty are atypical either because of minimal surface stratification or because of the presence of many multinucleated cells (Fig. 5 A and B). There were also forty cases of probable, three of questionable, and two of possible carcinoma in situ. These forty-five equivocal cases are not included in the statistical data given in this paper but were reviewed as part of this study. Because of the presence of variable degrees of anaplasia those excluded cases are still of interest to follow since anaplasia is occasionally followed by cancer (Fig. 6) and frequently persists even after a cancer is destroyed locally.

\*A good duplicate of this biopsy punch is about to be produced by Kny-Scherer Co., New York, N. Y.

a constant figure of about 1.2 per cent in cervixes regarded as benign but diseased. It must be emphasized that our clinical criteria have been relatively constant during this ten-year period.

The incidence of invasive cancer of the cervix in a general hospital, according to Meigs,<sup>18</sup> is 1.6 per cent. Carcinoma in situ was found in 3.9 per cent of 1,200 clinically benign cervixes examined after complete hysterectomy by Pund and Auerbach.<sup>10</sup> In this clinic where total hysterectomy is routine,

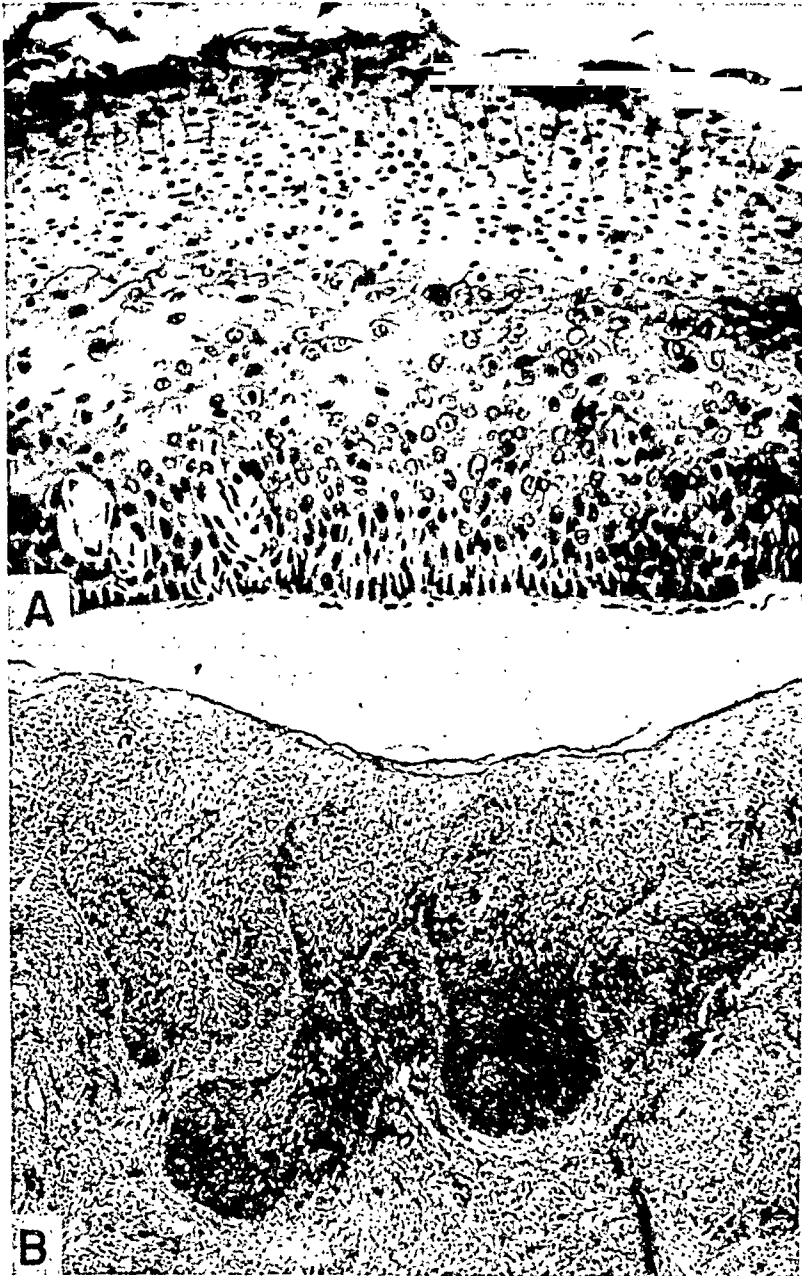


Fig. 6.—From a case of carcinoma of cervix progressing from anaplasia to stromal invasion within twenty-seven months.

A, Original biopsy showing anaplasia of basal half of epithelium but with superficial portion keratinized and moderately well differentiated. S-43-1931. ( $\times 300$ .)

B, Cervix at hysterectomy, twenty-seven months after original biopsy (Fig. 6 A) showing obvious epithelial malignancy with early stromal invasion. Note that there is some superficial keratinization. S-45-3137. ( $\times 125$ .)



been cauterized and followed until healed. Fifteen years ago only those cervixes which were grossly suspicious of cancer or did not heal after cauterization were biopsied, to wit, case No. 18737 (first case report). Because of this unintentional mistake carcinoma in situ was observed to progress to invasive cancer which taught us the value of biopsy before treatment and led to the deliberate experiment in 1937 (second case report). Routine biopsy then became the rule in the clinic. This procedure has furnished us with an incidence rate among women seeking aid for a variety of reasons in a large and exclusively gynecological clinic.

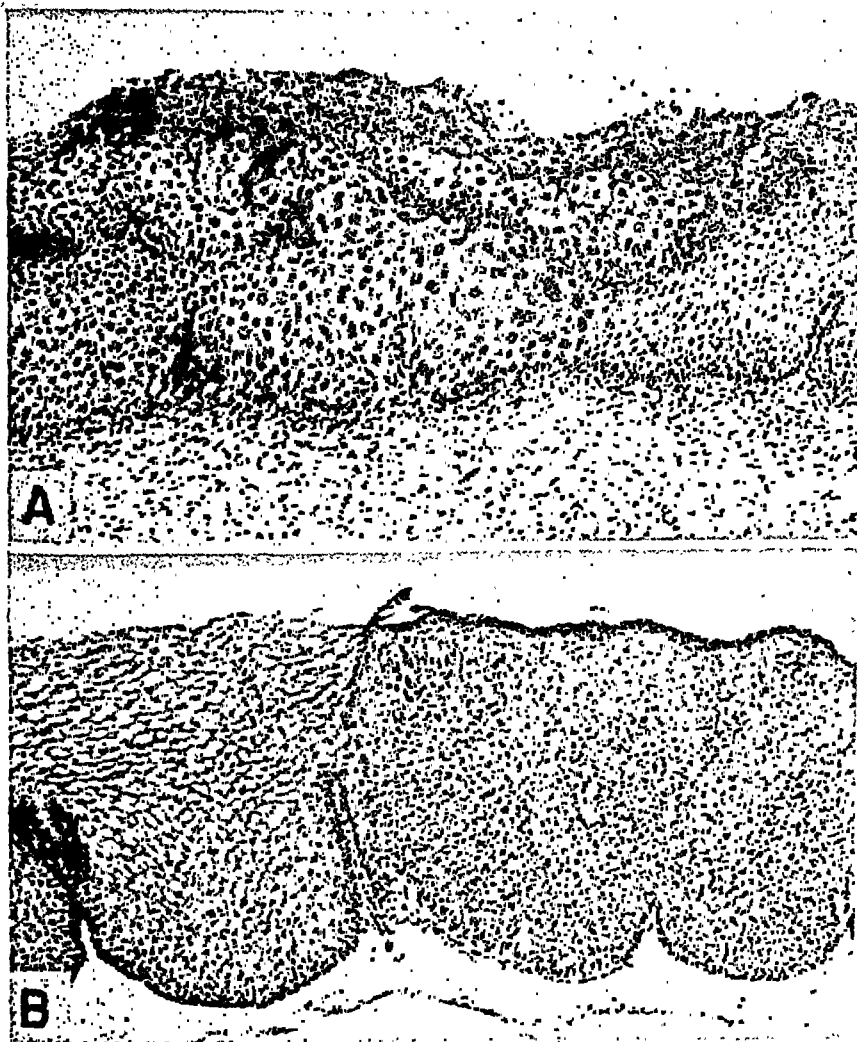


Fig. 5.—Examples of atypical carcinoma in situ of cervix.

A. A medium-power view of biopsy from portio vaginalis showing lack of differentiation, variation in cell size, and staining reaction together with the presence of multinucleated cells. S-40-2835. ( $\times 150$ .)

B. A medium-power view of biopsy from portio vaginalis showing slight surface keratinization but in general little differentiation. Note sharp line of demarcation between suspicious epithelium on right and normal tissue on left. Elsewhere in the cervix a biopsy showed typical carcinoma in situ. The latter was still present following hysterectomy. S-45-734. ( $\times 150$ .)

Thus, in 1937, 151 cases were biopsied in the Out-Patient Department, and two were found positive for carcinoma in situ (1.32 per cent), whereas, in 1946, biopsies done on 955 ambulatory patients yielded eleven cases (1.15 per cent). In our clinic, therefore, the incidence of the disease has remained at



for many generations, it has failed to increase greatly the cure rate for cancer of the cervix. It is not surprising, therefore, that 94 per cent of the patients in this series had cervixes which were regarded as normal or benign with eversion, erosion, laceration, hypertrophy, or leucoplakia. The Schiller test proved to be invaluable in pointing out the malignant areas in many of these benign appearing cervixes.

TABLE II. GROSS APPEARANCE OF CERVIX

		NO. OF CASES	PER CENT
Laceration with eversion	49	} "Erosion" 107	79.3
Erosion	48		
Hypertrophy with erosion	10		
SUSPICIOUS "erosion bleeds easily"		8	5.9
NORMAL		9	6.7
Leucoplakia		5	3.7
Cervical polyp	3	6	4.4
Atresia	1		
Decubitus ulcer (procidencia)*	1		
Inadequate description	1		
Total		135	100.0

\*The carcinoma in situ was on the opposite side of the cervix from the decubitus ulcer.

During the past ten years approximately 12,000 cervixes have been studied clinically as well as pathologically. First, and perhaps foremost, among the impressions gained by this experience is that many of the so-called "erosions" commonly regarded as the sequelae of childbirth are, in fact, of pre-existing congenital type, aggravated perhaps by the trauma of labor. Eight of the fifteen patients with carcinoma in situ who had never been pregnant had such a congenital erosion. In only one of those eight cases was the lesion suspicious because it bled easily; yet, it appeared to be a simple congenital erosion which Novak<sup>20</sup> states is of no clinical significance.

It is obvious to us after a review of these cases that there is no characteristic gross appearance of carcinoma in situ of the cervix. Only eight of the 100 cases diagnosed by biopsy were regarded as suspicious clinically, and in none of the 35 cases found incidentally was the possibility of malignancy entertained preoperatively. Yet the majority of these patients were examined by two or more "early-cancer conscious" gynecologists. The diagnosis was established in 100 cases by routine biopsy (usually at 6 and 12 o'clock) of benign appearing cervical lesions. Thus, approximately 8,333 cervixes were biopsied to detect those 100 cases of early cancer (1.2 per cent positive biopsies). With the current laboratory charge of \$6.00 per case, it would cost \$500.00 to find one easily curable cancer. This is a very reasonable price to pay.

### Microscopic Appearance

The classification of the microscopic appearance of the squamous epithelium of the cervix in its various gradations from benign to malignant as used in this laboratory are as follows: 1. Basal cell hyperactivity or hyperplasia as described by Te Linde.<sup>16</sup> 2. Anaplasia in three degrees classified as "possible," "questionable," and "probable" carcinoma in situ. 3. Definite carcinoma in situ.

"Anaplasia of repair" is sometimes confused with noninvasive cancer. This type of anaplasia is characterized by increased mitotic activity, slight variation in nuclear chromatin content and size of the nuclei, but the basal nuclei are orderly, and the epithelium differentiates normally.

cervical tissue from 2,262 cases was examined microscopically in 1946 (complete cervix 863; biopsy 1,399). Among the 2,262 cases there were seventy-five invasive cancers (3.3 per cent) and nineteen definite carcinomas in situ (0.84 per cent). Combining the definite with the equivocal "in situ" cases there were twenty-eight, or 1.24 per cent, a figure which approaches but does not exceed the incidence of the advanced form of the disease. The lower rate of 0.84 per cent among the total number of cervixes examined as compared to 1.15 per cent among the Out-Patient Department biopsies is accounted for by the fact that many clinically normal cervixes are removed by total hysterectomy whereas the Out-Patient cases are a selected group of abnormal cervixes.

In this clinic, therefore, carcinoma in situ of the cervix has occurred at a constant rate for a period of ten years, and its incidence is consistent with but a little less than that for invasive cancer in a large general hospital population.

### Age Incidence

Since carcinoma in situ may exist for a number of years before it becomes an invasive lesion, it is not surprising that the average age for this series of 135 cases is 38.7 years. The largest number of patients (thirty-three) occurs in the 30- to 35-year-old group (Fig. 7). Thus, the average age is 9.3 years less than the accepted average age of 48 years for frank cervical cancer.

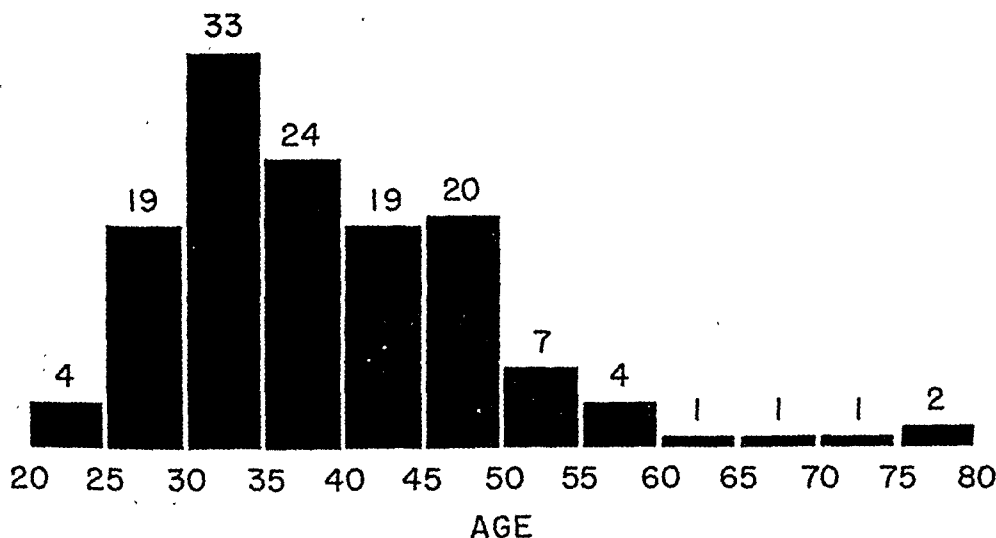


Fig. 7.—Age distribution of 135 cases of carcinoma in situ. Average age 38.7 years as compared to 48 years for invasive cancer.

### Symptoms

With respect to principal symptoms, 46 per cent of the cases had no complaints referable to cervical disease. Twenty-four per cent complained of or admitted to having leucorrhea, while 30 per cent had abnormal bleeding. The latter may have originated in the cervix because it was either postcoital, intermenstrual, or postmenopausal bleeding.

### Gross Appearance

While a maximum of 54 per cent of the patients had symptoms potentially referable to the cervix, only 6 per cent of the 135 cases had lesions suspicious of malignancy, that is, cervixes which bled easily on manipulation (Table II). Although biopsy of all suspicious lesions of the cervix has been the teaching

smear gave the first clue to the possibility of malignancy. Positive Papanicolaou smears were obtained on three occasions at monthly intervals. The patient had no symptoms, and the first smear was taken merely as part of a routine examination at her request to exclude cancer. An office curettage of the cervical canal revealed cancer in situ. Then a dilatation and curettage was negative, and four cervical biopsies taken in the operating room under anesthesia failed to show cancer (none of the biopsies contained endocervical epithelium but just portio epithelium). Hysterectomy, performed two months after the negative dilatation and curettage, and three months after the positive office biopsy, revealed a carcinoma in situ of the cervical canal with gland involvement.

TABLE III. ACCURACY OF PREOPERATIVE BIOPSIES (2 OR MORE) IN 54 CASES OF HYSTERECTOMY

BIOPSY	NO. CASES	HYSTERECTOMY
Probable carcinoma in situ	3	Surface carcinoma in situ (2) Gland* involvement (1) Chronic cervicitis (3) (cauterized preop.)
Surface carcinoma in situ	24	Anaplasia (4) (cauterized preop.) Surface (10) Gland involvement (7) Chronic cervicitis (radium) (1) (cauterized) (3)
Carcinoma in situ with gland and ? stromal invasion	27	Anaplasia (cauterized) (1) Surface only (1) Gland and ? stroma (19) Definite early invasion (2)

\*Surface carcinoma in situ with down growth into cervical glands.

Foote and Stewart<sup>21</sup> recently demonstrated that the lesion was inaccessible to the biopsy punch in two out of twenty-seven cases. Endocervical curettage is necessary for these rare cases. These authors also graphically demonstrated that routine biopsy at 6 and 12 o'clock would reveal the disease in only twenty out of twenty-seven cervixes (74 per cent). Biopsies should not be done routinely at 6 and 12 o'clock. They must be taken as indicated by the Schiller test and they must contain the junction of the nonstaining squamous epithelium and the erosion. If the Schiller test is negative, then the erosion alone is all that is necessary to biopsy. In this clinic we consider any exposure of the glandular epithelium due to laceration of the cervix under the same category as an erosion, and these cases are biopsied routinely. A recent example verifying the value of this procedure is a mother of eight children whose cervix was cauterized post partum (without biopsy) two years before we saw her. The cervix was deeply lacerated, but due to cauterization only a very small area of "glandular" epithelium was visible. Biopsy of this area and the cervix, itself, after hysterectomy showed definite carcinoma in situ.

#### Microscopic Extent of Disease

The result of the microscopic study of the entire series is shown in Table IV, which lists the morphological variants or extent of the disease. In all cases there was surface involvement, but in 50.4 per cent the malignant epithelium was confined entirely to the surface. On the other hand, 20.7 per cent of the cases showed definite extension of the neoplastic epithelium into the glands entirely replacing on occasion the glandular epithelium. The authors

In "basal cell hyperactivity" the lower one-third or one-half of the epithelium is definitely anaplastic. There is no orderly arrangement of the basal nuclei. The nuclei of this anaplastic layer are hyperchromatic, variable in size and shape, and their long axes are disorderly. The nucleoli are large. The size of the nucleus is larger in relation to the cytoplasm than in normal or reparative epithelium. Mitoses are increased in number and are found anywhere in the involved epithelial layer, but their number is relatively unimportant. The failure to differentiate is the most important feature. The superficial one-half or two-thirds of the epithelium differentiates normally, but the basal portion looks malignant.

The three gradations of anaplasia (possible, questionable, and probable carcinoma in situ) are characterized by a more advanced form of basal cell hyperactivity involving the entire thickness of the epithelium except for a few layers of surface cells. The degree of anaplasia depends upon the amount of hyperchromatism and lack of differentiation. The gradation of the three stages is difficult to describe except by comparing one slide with another. Some just look more malignant than others.

Carcinoma in situ is completely undifferentiated squamous epithelium forming an intact layer of cells covering the portio vaginalis of the cervix, extending on occasion to the vagina but more frequently spreading upward into the cervical canal. In about 50 per cent of the cases it extends into the cervical glands. There usually is a sharp demarkation between the normal and malignant surface epithelium. On occasion there is an oblique line such as Schiller described although the transition between the malignant and benign epithelium may be gradual. Carcinoma in situ replaces the columnar cells of the endocervix or of the cervical glands as it advances. This is in contrast to the undergrowth which takes place in squamous metaplasia or epidermatization. The benign undergrowth of squamous metaplasia as distinguished from the total replacement of the endocervical epithelium by carcinoma in situ was first noted over twelve years ago, and no exception to the rule has been found to date.

### Accuracy of Biopsy

How accurate are our biopsies in detecting these early and frequently small cervical carcinomas? The answer to this question involves too many variables to make it universally applicable. It requires the co-ordinated efforts of: 1. The clinician with his correct evaluation of the cervix and the Schiller test and his dexterous use of the biopsy punch; 2. The technician and her accuracy in embedding, cutting, and staining a small piece of tissue; and 3. The pathologist with his ability to recognize carcinoma in situ and lesser degrees of anaplasia which indicate repeated biopsies. The first biopsy in 13 of the 100 cases diagnosed by biopsy did not show definite carcinoma in situ (epidermoid hyperplasia, one; anaplasia, nine; and questionable or probable cancer in situ, three). In the thirteen cases the pathologist (P.A.Y., one; A.T.H., twelve) recommended a repeat biopsy which then showed the disease. This demonstrates the value of establishing the diagnosis before treating a diseased cervix and of secondary biopsies when the first shows anaplasia.

An analysis of fifty-four cases with two or more biopsies before hysterectomy shows the accuracy of cervical biopsy in this clinic (Table III). In two cases\* only was the disease definitely more advanced than we anticipated.

In only one of the 135 cases was the disease confined to the limits of the cervical canal. This case is the only one in this series in which the vaginal

\*Both cases are reported in detail under Microscopic Extent of Disease: S-45-233 and S-46-189.

serial block study of the entire cervix. While there is definite invasion, these two cases are so early that they are not included in the group of typical cancers of the cervix in this hospital (to be reported in the near future by Smith).

Ten cases are included in this series showing only the minimal criteria of carcinoma in situ, that is, marked basal cell activity with some degree of stratification. There are four additional cases, however, whose preoperative biopsies show only the minimal criteria, but the hysterectomy specimens show definite carcinoma in situ, one of which also had early invasion. The first biopsy in thirteen cases showed various degrees of anaplasia; yet, the second set of biopsies showed definite carcinoma in situ. One of these cases at hysterectomy showed early invasion.

In this series of cases eighty-three complete cervixes were examined microscopically. The diagnosis of carcinoma in situ had been made preoperatively by biopsy in fifty-six of these cases, but the disease had been "cured" by the preoperative treatment in eleven (cauterization, ten, and irradiation, one). In five of the eleven "cured" cases anaplasia of the cervical epithelium was present showing a malignant tendency to persist.

Serial block, or step section, study was done on eighteen complete cervixes as shown in Table V. Extension of the tumor from the cervix to the vagina was found in only one case in the entire series (Fig. 5A and B).<sup>2</sup>

TABLE V. STEP SECTION STUDY OF 18 EXCISED CERVICES

NO. OF CASES	BIOPSY	HYSTERECTOMY
8	Early invasion	Early invasion
4	Surface only	Surface only
2	Glandular involvement	Early invasion
1	Anaplasia—no tumor	Early invasion
3	Surface	No tumor*

\*Cervix cauterized 11 days, 1 month, and 3 months before hysterectomy.

### Vaginal Smear Correlation With Extent of Disease

Vaginal smears were studied in thirty-one cases with a 71 per cent degree of accuracy on the first or second smear and 61 per cent on the first smear alone. When these cases, however, were segregated as to the extent of the disease (Table VI), there was a 93 per cent degree of accuracy in the cases with gland or early stromal involvement and 53 per cent for cases with surface involvement only. The fact that carcinoma in situ of the cervix produces the same cytological picture in vaginal smears as cancer is just about the last bit of evidence needed to clinch the true nature of the disease, which has been doubted by so many pathologists for so long a time.

TABLE VI. RELATION OF VAGINAL SMEAR DIAGNOSIS TO EXTENT OF DISEASE IN 31 CASES

EXTENT OF CARCINOMA IN SITU	VAGINAL SMEAR	
	CORRECT	FALSE
Surface involvement only	9 53 per cent	8 47 per cent
Surface involvement plus glands and stroma	13 93 per cent	1 7 per cent
Total	22	9

\*Since this study was concluded, two additional cases of extension to the vagina have been observed. In both cases the Schiller test delineated the malignant vaginal epithelium. In one of these cases a radical panhysterectomy with en bloc pelvic node resection was performed removing two-thirds of the vagina as well. Twenty-four lymph nodes were negative.

do not regard this glandular involvement as evidence of invasion which is contrary to the opinions of Te Linde, Novak, and Robert Meyer.<sup>22</sup> We thus concur with the opinions expressed by Ewing and Mallory in their previously quoted personal communications. Glandular involvement, therefore, merely indicates a more extensive replacement of the endocervical epithelium by carcinoma in situ.

TABLE IV. MICROSCOPIC EXTENT OF CARCINOMA IN SITU

	NO. OF CASES	PER CENT
Involvement of surface epithelium only	68	50.4
Involvement of glands	28	20.7
Glands and probable invasion of stroma	20	14.8
Probable or questionable early stromal invasion (alone)	12	8.9
Definite early stromal invasion (too early for frank cancer)	5	3.7
Carcinoma in situ pattern with definite cancer	2	1.5
Total	135	100.0

Thirty-seven cases (27.4 per cent) with or without glandular involvement exhibited questionable or minimal stromal invasion by the neoplastic epithelium. It was demonstrated in five of these thirty-seven cases after "step section" study of the entire cervix that such invasion was definite but early. Since a majority of pathologists would not accept these five cases in a group of true cancer patients, they are included in this series. Thus, they constitute a transitional group between true carcinoma in situ and carcinoma of the cervix. One of these five cases had leucoplakia and anaplasia of the cervix in September, 1943 (Fig. 6A). She refused treatment and was not seen again until October, 1945, two years and one month later. At this time a second biopsy was performed which showed a "probable carcinoma in situ" (S-45-2774). The cervix at hysterectomy, however, showed carcinoma in situ plus extension to the vagina and definite but early stromal invasion (Fig. 6B). Therefore, we feel that this case can be included in this series as one which was followed and observed to progress from anaplasia of the cervix in a leucoplakic area to carcinoma in situ and finally to an early invasive lesion. The remaining four of these five cases showed even less stromal invasion than the one illustrated.

The final two cases which are listed in Table IV as showing the carcinoma in situ pattern with definite invasion must be considered individually. One case (S-45-33) showed carcinoma in situ on the original biopsy. After the hysterectomy the cervix was cut into eight blocks. Four of the slides showed no tumor, two carcinoma in situ with glandular involvement, one only surface involvement, while the eighth slide showed definite early invasion. The second case (S-46-189) had two biopsies from an innocent appearing erosion on the posterior lip of the cervix. Both slides presented a typical picture of carcinoma in situ. Nine days later, at which time the vaginal smear was negative, three additional biopsies showed carcinoma in situ with gland involvement. Twenty-two days later a hysterectomy was performed. She was then fourteen days overdue, and pregnancy was probable. The vaginal smear taken that day was positive, and the hysterectomy specimen showed an early Grade II squamous cell carcinoma of the cervix and a normal pregnancy four weeks of age. These two cases are included in this series to demonstrate forcibly two important facts: 1. Typical carcinoma in situ must be regarded as a malignant disease of the cervix. 2. The absence of invasion in a cervix showing carcinoma in situ in one area can be demonstrated only by complete

eight, and six months, respectively, before radical therapy; hysterectomy in two cases and irradiation in the third, and they are alive and well five, eleven, and two years later.

### Pregnancy After Cauterization for Carcinoma in Situ of Cervix

Six patients have become pregnant among the group of twenty-nine cases (Table VII) who apparently have been cured by cauterization of the cervix; four had normal living children, one miscarried, and one patient had a three months' gestation as of April 1, 1949. One patient was pregnant a second time and was due to deliver in August, 1949. One of the above four women who have had normal living children has since had a hysterectomy for a pseudomucinous cystadenoma of the ovary. Her cervix showed no disease.

The miscarriage occurred in a 31-year-old patient who sought advice because of leucorrhea for many years and postcoital bleeding and sterility since her marriage one year before. There was a positive Schiller test around the periphery of a wide congenital erosion. Biopsies at 1 and 5 o'clock showed chronic cervicitis with squamous metaplasia and anaplasia. One month later biopsies at 1, 7, and 10 o'clock showed carcinoma in situ with benign epidermatization of the glands. The vaginal smear at this time was positive. The condition was explained to the patient and her husband, and they preferred conservative treatment in the hope that they might have children. Three more biopsies were taken, all showing carcinoma in situ. The cervix was thoroughly coagulated in the Out-Patient Department, and two months later the vaginal smear and biopsy were negative. One year later (October, 1947) she was admitted to the hospital because of an incomplete spontaneous abortion. At the time of the curettage a cervical biopsy was taken which showed chronic cervicitis with squamous metaplasia. She is still under observation and will be followed indefinitely. This is the only patient deliberately treated by cauterization.

Still another patient, a mother of two children, had a repair of a large cystocele and rectocele at the age of 22 years. An erosion of the cervix was biopsied and cauterized at the same time. The biopsy showed invasive cancer, early, but too definitely invasive to include in this series. One year later her cervix was normal by biopsy and Schiller test. Then she became pregnant. A biopsy at three months was negative, but she had an induced abortion and died of septicemia in a hospital in a neighboring state. Autopsy showed no cancer. Apparently she had been cured of cancer by cauterization.

The experience with these cases shows that it is possible to preserve reproductive function in young women and safe for them to have children if there is no evidence of invasion or persistence of the disease after cauterization and repeated biopsies. However, if repeated biopsies show that the disease is still present and there is gland or early stromal involvement, it is dangerous to attempt conservative therapy.

### Treatment and Results

Table VIII shows the final treatment for the entire series thus far including the four trachelorrhaphy patients whose original diagnosis of carcinoma in situ was missed. They were subsequently treated by irradiation for clinical cancer. Six patients had radium and x-ray therapy in addition to complete hysterectomy. Irradiation after vaginal or abdominal total hysterectomy is considered unnecessary at the present time. Amputation of the cervix was performed on six patients, two of whom had postoperative irradiation, which is necessary if the extirpated cervix shows incomplete removal of the disease. At the present time, however, it is felt that hysterectomy is preferable for these cases.

### Results of Cauterization of the Cervix

In the early days of this study, five to ten years ago, the rule to biopsy and have a pathological diagnosis before treating an "eroded" cervix was not followed strictly as it is at the present time. Thus, the great majority of the forty-three cases treated originally by cauterization were cauterized at the time of the original set of biopsies. Only one was cauterized deliberately after the diagnosis had been established.

Sixteen of the forty-three cases were treated five to twelve years ago, and all are alive and free of disease at the present time, but four of the sixteen were not cured by cauterization. These four cases, in whom the disease persisted after cauterization as shown by biopsy, were treated by hysterectomy or radium one, one and one-half, eight, and fourteen months later and are free of disease, nine, eight and one-half, eleven, and five years postoperative. Of the twelve cured cases two had a hysterectomy three and four months after cauterization for "cancer hysteria," a third for functional flowing six years later, and no cancer was found in their cervixes. Nine of the twelve cured cases have had no further treatment except repeat biopsies and vaginal smears which have been negative.

Twenty-seven of the forty-three cauterized cases have been followed less than five years (sixteen months up to four and one-half years), but the authors feel reasonably certain of the final results for the entire group of forty-three because of the careful follow-up study by smears and biopsies. To date, of the forty-three cauterized cases, eighteen have had a hysterectomy, two have been treated with radium, and twenty-three have had no other treatment. In six of these eighteen hysterectomy specimens there was no cancer.

The study of the forty-three cases originally treated by cauterization gives us a definite working plan to follow in advising treatment for each individual case. This plan is the result of comparing the end results with the microscopic extent of the carcinoma in situ. Thus, 85 per cent of twenty-seven cases (Table VII) have been cured when the disease was localized to "surface involvement only," whereas, only 37 per cent of sixteen cases were cured when the disease had spread to the cervical glands with or without minimal stromal invasion. If multiple biopsies and endocervical curettage show no glandular involvement and there is a desire to preserve reproductive function, that patient may be offered cauterization with an apparent 85 per cent chance of cure. If the treatment fails to cure the disease as determined by biopsies two to six months later, her life has not been jeopardized by the delay while attempting conservative therapy. On the other hand, if the cervical glands are involved or there is early or even questionable stromal invasion, conservative therapy (cauterization or sharp conization) may be offered although it is not likely to produce a cure. The delay of two or three months, however, will not jeopardize the patient.

TABLE VII. EXTENT OF DISEASE IN RELATION TO RESULTS FROM CAUTERIZATION OF CERVIX (43 CASES)

EXTENT OF CARCINOMA IN SITU	APPARENTLY CURED		NOT CURED	
Surface involvement only	23	85 per cent	4	15 per cent
Surface involvement plus glands and stroma	6	37 per cent	10	63 per cent
Total	29*		14†	

\*Determined by subsequent biopsies and vaginal smears (23) or hysterectomy (6).  
†Determined by subsequent biopsy; 2 treated with radium, 13 by hysterectomy.

A complete hysterectomy was performed or radium applied within three months on eleven of the fourteen cases not cured by cauterization (Table VII). The other three cases were followed without further treatment for fourteen,



other two polypi and a cervical biopsy removed at the time of radium treatment showed no cancer. In spite of these negative findings, she received x-ray therapy (6,000 r.u.) as an ambulatory patient, and died of diabetic coma two days after the last x-ray treatment. It seems fair to assume that x-ray sickness precipitated the diabetic complication because she had been able to control her diabetes easily for several years. Here again, as in the previous case, it is suspected that the pathologist's report was not read in detail.

Table IX lists the type of treatment and results in detail of sixty-nine patients in this series who were treated before February, 1944. All except two have been followed and examined for from five to sixteen years (excluding four who died under five years). Two of the hysterectomized patients have not been followed beyond three months and one year, respectively, because they are untraceable.

TABLE IX. TREATMENT AND RESULTS FIVE OR MORE YEARS POSTOPERATIVE  
(69 CASES)

Trachelorrhaphy (mistake in original diagnosis)	4 cases
3 died of cancer of the cervix 4 years, 3 months; 6 years, 7 months; and 8 years, 3 months.	
1 treated with radium 4 years, 8 months postoperative for cancer of the cervix. Alive and well 16 years.	
Excision of cervical polyp	1 case
Alive and well 12 years, 8 months postoperative.	
Radium with or without x-ray	18 cases
1 case, recurrence 3 years postoperative. Died of cancer of the cervix 5 years, 6 months postoperative.	
1 case died 1 year postoperative of irradiation complications.	
1 case died 2 years postoperative of pulmonary tuberculosis.	
15 cases alive and free of disease 5 to 15 years postoperative.	
1 case died of heart disease 5 years, 9 months postoperative.	
1 case died 7 years, 7 months postoperative of cancer of the breast (2 years postoperative).	
Amputation of cervix	3 cases
1 case, age 75 years, died 3 years, 9 months postoperative of heart disease.	
2* alive and well 9 and 11* years postoperative.	
Cauterization of cervix (all alive and well 5 to 12 years postoperative)	16 cases
4 cases not cured.	
1 case, radium 8 months later. Alive and well 11 years postoperative.	
1 case, radium 6 weeks later. Alive and well 8 years, 6 months postoperative.	
2 cases complete hysterectomies 1 month and 14 months postcautery. Alive and well 9 and 5 years postoperative.	
12 cured: Alive and well 5 to 12 years postoperative	
9 no further treatment except biopsies and smears.	
3 hysterectomies 3 months, 4 months, and 6 years postcauterization—no cancer.	
Complete hysterectomy	27 cases
24 alive and well 5 to 15 years postoperative.	
1 died of cancer of endometrium 5 years postoperative (autopsy).	
2 cases alive and well 3 months and 1 year (not followed).	

\*One case, a deliberate experiment, followed 1 year after diagnosis was made, and definite invasive cancer of the cervix found in amputated cervix.

The follow-up studies on the more recent cases in this series in the past five years amply justify the finely separated histological classification used in this laboratory for the suspicious lesions and early malignancies of the cervix. By repeated biopsies, we have observed basal cell activity apparently progress to anaplasia and possible or even questionable carcinoma in situ. Basal cell activity, anaplasia, and definite carcinoma in situ may be seen in one cervix.

TABLE VIII. ULTIMATE TREATMENT OF ENTIRE SERIES

TREATMENT	NO. OF CASES	DEATHS		
		CANCER OF CERVIX	OTHER CAUSES	FROM TREATMENT
Complete hysterectomy (69)	75		1	
Complete hysterectomy plus radium and x-ray (6)				
Amputation of cervix (4)	6		1	
Amputation of cervix plus irradiation (2)				
Vaginal hysterectomy	2			
Supravaginal hysterectomy plus radium	3	1		
Radium	12		3	
Radium and x-ray	4			2
Cauterization and x-ray	1			
Cauterization of cervix	23			
Trachelorrhaphy*	4	3		
Polypectomy	1			
No treatment	4			
Total	135	4	5	2

\*Original diagnosis missed. All developed invasive cancer  $3\frac{1}{2}$  to  $6\frac{1}{2}$  years later and then were treated. Only one survivor.

In twenty patients the disease was treated primarily by irradiation; supravaginal hysterectomy followed by radium, three cases; radium alone, twelve cases; radium and x-ray, four cases; and cauterization and x-ray, one case. Six of these patients are now dead; one from cancer of the cervix; two from irradiation complications; and three from other causes—pulmonary tuberculosis, heart disease, and cancer of the breast.

The above death from carcinoma of the cervix was a 30-year-old patient treated in 1929. Biopsy (one specimen) of the cervix and cauterization were done at the time of a supravaginal hysterectomy for fibroids and endometriosis. The first sections of the cervix were suspicious, but additional sections showed definite carcinoma which we now interpret as carcinoma in situ involving the glands. However, in 1929, another pathologist said, "Probably not malignant." A single application of radium (4,800 mg. hr.) was given one month postoperative at which time the cervical stump was described as well-healed and the pelvis negative. Three years later she was treated at the Pondville State Hospital for an "extensive recurrence" and died five and one-half years after the original treatment.\* Invasive cancer must have been present elsewhere in her cervix, but the biopsy specimen showed only the "surface coating" nearby.

The first death attributable to treatment per se occurred in July, 1944, in a patient treated in December, 1943. A biopsy showed carcinoma in situ involving the glands was taken at the time of a repair operation and cauterization of the cervix. From then on everything concerning her treatment can be criticized. Two weeks later, without another biopsy, she was given 3,200 mg. hr. of radium followed by x-ray therapy (4,800 r.u.). Thirty-five days after the one and only biopsy, the second dose of radium (4,000 mg. hr.) was applied. Death occurred eight months after treatment of pelvic abscess and intestinal obstruction attributable to irradiation.

The second death associated with treatment also occurred in 1944. One of three cervical polypi was removed in the Out-Patient Department and showed carcinoma in situ involving the glands. The patient was admitted to the hospital, and 3,000 mg. hr. of radium was applied to the cervical canal. The

\*Reported by Smith and Pemberton in 1934.

of the cervix. Cases have been observed to progress from "marked basal cell hyperactivity" to anaplasia and eventually to definite carcinoma in situ. Anaplasia of the squamous epithelium of cervix has been observed in this series to progress to early invasive cancer. In one deliberate and five unintentional clinical experiments carcinoma in situ has been seen to progress to invasive cancer in from eleven months to over six years.

The fact that this disease has been found to occur at a constant rate of approximately 1.2 per cent in routine biopsies of diseased but clinically benign cervixes during a period of ten years proves that it is a disease entity which occurs at a regularly predictable rate. Since it occurred in women whose average age is about nine years less than that for frankly invasive and clinically obvious cancer of the cervix, its long latent period is evident. It is a well-known fact that some cancers progress faster than others, and so it is with carcinoma in situ of the cervix. To this present day we do not regret or fear studying a case up to one year before deciding upon the type of treatment. It must be emphasized, however, that the evaluation of a case must be done by frequent and multiple biopsies aided by the Schiller test as well as endocervical curettage.

In these cases the chief responsibility rests upon the accurate interpretation of the cellular morphology of the biopsy specimen by the pathologist. On the other hand, the careful selection of the biopsy site by the clinician and his dexterity in performing the biopsy so as to include, undamaged, the exact area intended are of equal importance. Occasionally the pathologist will report "portio epithelium only" or "endocervical epithelium only." These reports mean inadequate or improperly performed biopsies because the junction of the two cervical epithelia should be present in a perfect biopsy since most cancers begin at that junction.

Not infrequently slides are sent to this laboratory for an opinion after a diagnosis of carcinoma of the cervix has been made elsewhere. Some of these "consultation cases" are just carcinoma in situ with or without gland involvement. Radical treatment such as Wertheim hysterectomy or a full course of irradiation is, therefore, not justified unless further study reveals truly invasive cancer. Also, cervixes showing epidermatization or squamous metaplasia are confused with invasive cancer or carcinoma in situ with gland involvement. Treatment of any case should not be done until the disease is evaluated by at least a second set of biopsies and endocervical biopsy or curettage. All of us have made these mistakes, but with more experience they become less frequent.

The hysterical fear frequently aroused by the diagnosis of carcinoma in situ is without reason. There is no need to perform a hysterectomy immediately, or the next week, or the next month after the first biopsy. The case should be evaluated carefully first especially because this is a disease of younger women, many of whom want a child or more children (41.1 per cent under 35 years of age and 17.0 per cent under 30). When the disease is early (surface involvement only) cauterization or sharp shallow conization can be offered as a nonsterilizing treatment to these young women with an 85 per cent apparent chance of success. In this series eight patients have become pregnant of whom six have normal living children, one is normally pregnant at three months' gestation, and the eighth had a miscarriage. Pregnancy occurred in six of the eight patients after successful conservative treatment and in two in whom the disease either regressed or was cured by biopsy.

The problem of establishing the diagnosis of this early form of cervical cancer on a nationwide basis is a difficult one. Not many physicians have the time, equipment, or ability to perform selective cervical biopsies of all eroded

In July, 1943, a biopsy (S-43-1109) showed a very disturbing anaplasia of the cervix. The patient did not keep her appointment, and we did not see her again until February, 1946, when she had advanced cancer of the cervix and died in June, 1947. She had been treated elsewhere in July, 1945, two years after the biopsy. Because of lack of data this case is not included in the series although other cases (Nos. 83, 86, and 119) have shown apparent progression from probable carcinoma in situ to the definite disease with involvement of the glands in from two months to eleven months.

A study of the end results in relation to the type of treatment at the time or within two months of original diagnosis, gives us the most valuable information. Twelve cases received no treatment or inadequate treatment, five of whom developed invasive cancer eleven months to six and one-half years later; in two additional patients the disease persisted as shown by hysterectomy six and eleven months later; in four others\* it regressed, and in the final one the disease was cured by the removal of a cervical polyp (Table X).

TABLE X. END RESULT IN RELATION TO TYPE OF TREATMENT AT TIME OF ORIGINAL DIAGNOSIS

TREATMENT	NO. OF CASES	DEVELOPED INVASIVE CANCER	CARCINOMA IN SITU PERSISTED	CARCINOMA IN SITU CURED BY CAUTERY	CARCINOMA IN SITU REGRESSED AFTER BIOPSY
Adequate <sup>a</sup>	80	1 <sup>c</sup>	0	0	0
Inadequate <sup>b</sup>	5	4 <sup>d</sup>	0	0	0
None except biopsies	7	1 <sup>e</sup>	2 <sup>f</sup>	0	4 <sup>h</sup>
Cauterization	43	0	14 <sup>g</sup>	29	0
Total	135	6	16	29	4

a. Complete hysterectomy; amputation of cervix with or without irradiation; or irradiation alone.

b. Trachelorrhaphy 4 cases; Excision of cervical polyp 1 case—alive and well 12 years. 8 months.

c. 4800 mg. hr. radium 1 month after biopsy. Died of cancer of cervix 5½ years later.

d. Invasive cancer recognized 3½ to 6½ years later, treated with radium—1 survivor. Original diagnosis missed.

e. Deliberate experiment: developed invasive cancer 11 months later (alive 11 years postoperative).

f. Two cases had hysterectomy 6 and 11 months later.

g. Carcinoma in situ persisted as shown by biopsy or hysterectomy 2 weeks to 14 months later.

h. Carcinoma in situ regressed to anaplasia after second or third biopsy—2 cases followed through pregnancy.

One of the above untreated cases had negative vaginal smears and anaplasia of the cervix on two successive biopsies. She then became pregnant. In the second month a biopsy showed carcinoma in situ in one out of eight sections made from one biopsy, and the vaginal smears became positive and remained positive until the sixth month. During this time the innocent erosion became suspicious, and the Schiller test, previously negative, became positive. She had a normal delivery, her fifth, at full term. Six weeks post partum the cervix was practically normal, and the Schiller test and vaginal smear were negative. Anaplasia of the type we have seen progress to carcinoma in situ, however, still persists. She is now pregnant again.

### Comment

All of the evidence obtainable from this study and from the experience of such careful workers as Schiller, Te Linde, and Pund and Auerbach, point to the validity of the eventual clinically malignant behavior of carcinoma in situ

\*All four cases had positive vaginal smears, but their biopsies showed only the minimal criteria, i.e., surface differentiation. At this stage the disease may be reversible.

vaginal cuff is considered adequate treatment. The Schiller test helps to decide how much vaginal cuff should be removed. The authors do not feel that a Wertheim hysterectomy is necessary, or even TeLinde's modified Wertheim operation, if the cases are studied adequately before treatment. Irradiation therapy, although it will cure the disease, should be reserved for the rare poor-risk patient. No patient in this clinic has been treated by irradiation for carcinoma in situ since 1944, and the last two so treated are deeply regretted because they are the only fatalities due to treatment in this series.

### Summary and Conclusions

1. Six cases of carcinoma in situ of the cervix have been observed in this clinic to progress to invasive cervical cancer in from eleven months to six and one-half years. Three of these patients died of their cancer whereas three are living and well four, eleven, and sixteen years after treatment for the invasive carcinoma. One of the latter patients while under direct observation developed invasive carcinoma at the original biopsy site during a period of eleven months.

2. One case of "marked anaplasia" of the cervix was found to have cancer of the cervix two years later and died of cervical cancer two years after treatment. It is suspected that the original biopsy showing anaplasia was taken from the periphery of an invasive cancer although this was not suspected clinically.

3. "Basal hyperactivity," anaplasia, atypical or equivocal carcinoma in situ and definite carcinoma in situ may be found either together, separately, or in a cervix with obvious cancer. Although it is impossible to prove, cases have been observed which have seemed to progress through these stages of anaplasia and finally become carcinoma in situ.

4. Carcinoma in situ of the squamous epithelium of the cervix represents either malignancy in its early stage or noninvasive cancer at the periphery of an infiltrating lesion. Therefore, when it is found, invasive carcinoma must be ruled out by multiple biopsies or serial block study of the entire surface of the cervix.

5. If no invasion is found on the first or second biopsies, a deliberate study of the cervix may be done by repeated multiple biopsies and vaginal smears for at least six months with no risk to the patient. If the carcinoma in situ involves only the surface epithelium and does not involve the cervical glands, thorough destruction of the surface lesion by cauterization or complete excision by sharp conization will apparently cure 85 per cent such cases. Reproductive function, thus, may be preserved in young women. Those not cured by these conservative methods should have a simple total hysterectomy removing as much vagina as is indicated by the Schiller test. Removal of the ovaries is not necessary.

6. If after thorough study the carcinoma in situ is found to involve the cervical glands but there is no stromal invasion, a simple total hysterectomy is indicated.

or positive Schiller test cervixes as are done in this clinic. Nor are cervical biopsies very accurate in any clinic not highly specialized in this art as demonstrated by Fremont-Smith, Graham, and Meigs<sup>23</sup> at the Massachusetts General Hospital. They found in a general hospital that vaginal smears were far more accurate than biopsies which is exactly opposite to our findings. Vaginal smears, however, are reliable when the in situ cancer is more advanced, i.e., with gland involvement. Here again, very few physicians have at their disposal a reliable laboratory for the reading of vaginal smears so it is rather obvious that the majority of women cannot be given, at the present time, the advantage of early diagnosis by either biopsy or vaginal smear.

What then can be done to diagnose early cancer of the cervix while it is in the easily curable "in situ" stage? First of all, basal cell hyperactivity or anaplasia and carcinoma in situ have been found in this clinic at the periphery in many congenital erosions as well as in the post-partum erosions or exposed endocervix in lacerated cervixes. If these cases are not suspicious clinically, have no abnormal bleeding, and the Schiller test is negative, thorough cauterization without biopsy should be done. Such a cauterized cervix, after one adequate cauterization, should be restored to a normal appearing cervix inside of two to three months. By a "normal appearing cervix" it is meant that all of the erosion has been replaced by squamous epithelium which stains with Gram's iodine solution. If carcinoma in situ persists after cauterization, the Schiller test will be positive and/or some "erosion" still will be present. In these cases biopsy is mandatory.

With respect to the value of the Schiller test in this series, twenty-seven out of twenty-nine cases so tested had a positive test (93 per cent). More extensive application of the test in the past two years has verified this fact. Therefore, biopsy of all cervixes with nonstaining squamous epithelium should be mandatory in spite of the fact that over 90 per cent of positive Schiller test cervixes show only paraneukeratoses or other benign lesions. A physician cannot assure his patient that she does not have cancer of the cervix if there is an erosion or a positive Schiller test unless he has ruled it out by biopsy.

To prove that carcinoma in situ of the cervix may spontaneously regress is difficult because it is theoretically possible to remove the entire lesion in one biopsy. This apparently has been recently demonstrated in a cervix removed by hysterectomy a few days after the biopsy. In this series, however, there are four untreated cases in whom no cancer can be found by vaginal smear or biopsy one and one-half to two years after the original positive biopsy and definitely positive vaginal smears. A re-evaluation of the original slides in these four cases shows that all exhibit some surface differentiation which may represent the reversible stage of the disease. Their apparent regression, on the other hand, may mean that the entire lesion was removed. Whether these four cases have regressed or were cured by biopsy demonstrates the extreme importance of a calm and deliberate appraisal of all of these lesions before embarking upon radical treatment.

The careful and accurate study in cases of young women with child-bearing aspirations has been discussed. When the disease is found in women in the older age groups or in those patients, young or old, who have some other condition indicating a hysterectomy, it is just as essential to evaluate the extent of the disease. Invasive cancer must be ruled out before a simple total hysterectomy, with or without preservation of ovarian function, can be considered safe and the proper treatment. Because of the long follow-up on the twenty-four hysterectomized patients treated before 1944 (five to fifteen years) and because of the negative lymph nodes in three recent Wertheim hysterectomy cases, a routine total hysterectomy plus one centimeter of

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### Discussion

DR. GEORGE H. GARDNER, Chicago, Ill.—Probably we are still confused regarding certain aspects of this condition, but must agree that this portrayal of twenty-three years' experience at the Free Hospital helps to clarify some of the issues.

Carcinoma in situ was found in 1.2 per cent of their cervical biopsies taken routinely from every clinic patient with either an eroded, an everted, or a positive Schiller test cervix. The authors accept the incidence of invasive cancer of the cervix as 1.6 per cent, and, without further ado, assume that carcinoma in situ occurs at a regular predictable rate comparable to the incidence of invasive cervical cancer.

Next, the average age of their carcinomas in situ is 38.7 years; with TeLinde it was 37.1 years. Both groups consider it highly significant that there is a lag of about ten years between the average of in situ lesions and the average age of invasive cervical cancers.

The Boston group continues with additional data which suggest that carcinoma in situ may be an irreversible process; for example, they observed six carcinomas in situ which, within eleven months to six and one-half years, progressed to invasive cancer. Another patient originally showed only "marked anaplasia" but progressed to invasive cancer within two years and died of her cancer two years later. They have also found basal cell hyperactivity, anaplasia, atypical carcinoma in situ as well as definite in situ cancer, not only separately and together, but also in a cervix with obvious cancer. All of this suggests but fails to prove that carcinoma in situ is irreversible.

They are enthusiastic about the Schiller test as an aid in accurate delineation of surface lesions and for determination of the exact sites to be biopsied. They do not share Meigs' confidence in vaginal smears but they are ardent advocates of repeated biopsies, and I agree that every original diagnosis must be confirmed. However, I doubt the effectiveness of biopsies in determining the extent of the disease and the degree of invasion, and I suspect a lack of agreement among the authors on this point since their paper contains conflicting statements; for example, "the absence of invasion in a cervix showing carcinoma in situ in one area can be demonstrated only by complete serial block study of the entire cervix." With this I agree most heartily, but find difficulty in accepting the following: "If multiple biopsies and endocervical curettage show no glandular involvement, and there is a desire to preserve the reproductive function, that patient may be offered cauterization with at least a 75 per cent chance of cure." To go further, they may be justified in rejecting extension of surface cancer into cervical glands as evidence of invasion. But when one is seeking order out of chaos it is regrettable that they further complicate an already confused subject by introducing a rather complex histopathological classification for these lesions. Actually they suggest anaplasia as the name for those intermediate cases which are more extensive than basal cell hyperactivity but do not show involvement of all layers of the squamous epithelium, their definition of true carcinoma in situ.

7. At present all available evidence indicates that lymphatic spread does not occur from carcinoma in situ of the cervix. Therefore, pelvic lymph node dissection is not indicated in cases adequately studied before treatment is undertaken. A simple total hysterectomy for carcinoma in situ after only *one* biopsy is hazardous because invasive cancer has not been ruled out preoperatively.

8. Adequate evaluation and study of most of these cases can be done without hospitalization by the use of a good biopsy punch and an accurately interpreted Schiller test. Endocervical curettage, submitting blood clot as well as tissue, is an essential part of the study of each case.

9. A normal cervix is one completely covered with squamous epithelium which stains dark brown after applying Gram's iodine solution. No glandular epithelium should be visible except that inside the cervical canal. All others are regarded as abnormal and all erosions, lacerations with eversion, "spotty erosions" on hypertrophied cervixes and positive Schiller test areas should be biopsied. Carcinoma in situ is found in 1.2 per cent of such routine biopsies.

10. Only 6 per cent of the cases in this series had suspicious cervixes and 46 per cent were asymptomatic. Abnormal bleeding occurred in only 30 per cent of the cases.

11. Eight of fifteen cases who had never been pregnant had what appeared to be innocent congenital erosions.

12. The average age of women with carcinoma in situ of the cervix is 38 years, 41 per cent being under the age of 35 years and 17 per cent under thirty years.

13. Vaginal smears are reasonably accurate (93 per cent) when carcinoma in situ involves the cervical glands but will reveal only 53 per cent of those showing just surface involvement.

14. Pregnancy is not hazardous after curing carcinoma in situ of the cervix by cauterization. Six such patients in this series have become pregnant, four having had normal deliveries, one miscarried at three months, and the sixth is at present three months pregnant. Two untreated cases, whose disease has regressed or was cured by biopsy, have subsequently had normal children.

15. Five-year follow-up study on sixty-nine patients with cervical carcinoma in situ shows that none with adequate study before treatment has had a recurrence or died of the disease.

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to the patient and her family. Now, just how does Dr. Younge or anyone else break such information to the patient? This is a serious matter to these women and cannot be "laughed off." I feel sure that there are others here who would like the answer to my question.

DR. ARTHUR HERTIG.—I suggest that Dr. Younge, who is a good psychologist in regard to this problem of breaking the news to the patient, answer Dr. Matthews' question. Dr. Younge gets his patients to come back month after month, and moreover does not scare them to death when he tells them what the situation is in respect to the suspicious lesion.

DR. ISIDOR C. RUBIN, New York, N. Y.—At the beginning of my career I had the good fortune to study at the laboratory of Schottlaender under Von Rosthorn. The now famous book of Schottlaender and Kermauner on carcinoma of the uterus was published in 1912. It is a classic and as useful today as it was when published.

There were two schools of thought then as there are today. Schottlaender predicated that the epithelium of the vaginal portio underwent certain changes with atypicalism of the cells which he described as "unrest," all of which were beautifully illustrated by a number of the slides shown this morning. There was another school which claimed that these proliferative changes are due to some unknown stimulus not necessarily precancerous in nature. Further that we cannot speak about cancer lesions unless there is positive lymphatic invasion. Now we have carcinoma in situ which has been referred to by some as epithelioma of the cervix similar to basal epithelioma of the skin.

The question is, what to do when you come upon a smear which is positive? I had one patient upon whom I did a trachelorrhaphy and the report was carcinoma in situ. She refused further operation or treatment of any kind. According to her husband, she already had carcinophobia. I saw her the other day, eleven or twelve years older, and the cervix is just as good as it was then and the vaginal smear was negative. Incidentally, she had had about 14,000,000 units of female sex hormone over a period of eight or nine years which should have added theoretically to the cancer stimulation but did not. I believe a case like this, if at all possible, should be followed regularly as Dr. Younge has followed his. From my point of view, I would prefer to see these patients submit to operation when there are outspoken signs of cell atypicalism characteristic of early carcinoma.

DR. OTTO SCHWARZ, St. Louis, Mo.—I want to recall a paper read by Dr. Robert Crossen at the last meeting of the Society. He and his father have been doing routine conizations for benign lesions of the cervix. I feel that in cases of benign lesions of the cervix conization is indicated; microscopic sectioning will rule out any carcinoma and you can detect lesions such as have been discussed. When such lesions occur, you have done no harm and you have put the patient in a position where you can watch her or treat her further. At first glance this may seem radical but I feel very definitely that the procedure is prophylactic; you do no harm and the patient is made more complacent.

DR. W. G. COSBIE, Toronto, Can. (by invitation).—In the realm of cancer therapy at the present time, the most important factor is early diagnosis and when we are faced with the fact that present methods of treatment are reaching a plateau above which they seldom rise, it is natural that every effort should be made to obtain a diagnosis even before invasion has taken place. One hears much of the value of cancer prevention or detection clinics. In Ontario we have made a survey recently because we realized that the people who are coming to these clinics are nearly all from the better economic brackets. We found that to extend such a service to the whole province would cost about \$39,000,000 a year. We wonder if there are not better ways of spending the money which we have available for the diagnosis and treatment of cancer than in the widespread establishment of such clinics.

There is another phase of this question which is worthy of consideration. The vaginal smear has received such wide publication that not only patients but general prac-

If we are agreed that carcinoma in situ is cancer, then we are also agreed that effective treatment must eradicate the cancer. However, experience to date strongly suggests that it need not be so radical as for invasive cancer. Consequently total hysterectomy with removal of an adequate vaginal cuff seems to be satisfactory. Treatment of carcinoma in situ by cauterization alone was an interesting experiment but should not be continued irrespective of how efficient the subsequent follow-up may be. Furthermore, I cannot accept either trachelorrhaphy or conization alone as adequate treatment. And now that the Free Hospital has survived twenty years of therapeutic experimentation, I hope they will do more total hysterectomies for carcinoma in situ, a highly desirable policy since it would yield; (1) Better specimens for study; (2) adequate material to determine the extent of the disease and the degree of invasion, if any; (3) more evidence to justify anaplasia as a type of carcinoma in situ and to clarify its suggested subdivisions, and (4) last but not least, a larger series of cured patients.

DR. ARTHUR HERTIG, Boston, Mass.—We are trying to be rigid in our morphological criteria in diagnosing cervical carcinoma in situ. The situation is somewhat confused by differences of opinion regarding these morphological criteria of preinvasive cervical malignancy and furthermore by differences in terminology among those investigators who actually recognize that such a biological entity exists. One should, therefore, be careful to distinguish between such a terminological and biological argument.

Admittedly there are an insufficient number of cases which have been followed through the various stages of squamous cervical malignancy from anaplasia, surface carcinoma in situ, and subsequent glandular involvement to stromal invasion and true clinical carcinoma.

We have tried to give evidence that some of these anaplasias ultimately develop into carcinoma in situ or actual invasive carcinoma. We have not included in this series any cases in which anaplasia was the only diagnosis without further evidence of subsequently developing carcinoma in situ. Dr. Younge showed you merely one classic example. He could have shown others.

There are several variants of squamous carcinoma of the cervix and I am not always able to figure out which particular carcinoma in situ will go on to any given definitive squamous malignancy. The average Grade II type probably arises on the basis of the classic case Dr. Younge showed you since most of the carcinomas in situ are of that variety.

We do not believe that gland involvement constitutes true invasion because the morphologically malignant tissue is still within epithelial structures. Admittedly this is a later stage of carcinoma in situ but there is no stromal invasion since the basement membrane is still intact.

It should be emphasized that we do not believe that cauterization is the proper or even usual method of treating these patients. This study covers approximately twenty years and early in this period cauterization was done at the time the biopsy was taken. Such a case was, therefore, unsuitable for the study of the genesis of cervical malignancy. I think that cauterization is justified in the occasional case requiring conservation of reproductive function providing the surface epithelium is the only structure involved, the patient is young, the situation is explained to her and she desires to take the chance. These are individual matters which should be settled between physician and patient. In the deliberately cauterized cases which Dr. Young presented, the four patients who subsequently had living babies seems to justify that point of view.

DR. HARVEY B. MATTHEWS, Brooklyn, N. Y.—I have a question and I seek the answer from someone in this audience. The cytological problem and the biopsy have been given full evaluation but absolutely nothing has been said about the psychological problem in relation to the woman who has to be told that she has cancer. Dr. Younge showed data of a young woman who had had no symptoms referable to her pelvis but in the course of a routine physical examination vaginal cytology was done and "lo and behold" cancer in situ of the cervix was found. Finally hysterectomy was recommended. Imagine the shock

## RESULTS OF AN EXPERIMENTAL THERAPY OF CARCINOMA OF THE CERVIX\*

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IT IS generally agreed that irradiation therapy of cervical carcinoma offers the most effective therapeutic approach presently available. That it is not an ideal solution to therapy is obvious. But until a better approach becomes available, the therapeutic tools which are at hand must be used with a maximum efficiency. A great variety of techniques is being used. These show variations in time factors, in dosage and the accuracy with which this is determined and reported, in the relative stress given to x-ray and to radium and in the technical details of controls and patient care. It has been publicly stated that all of these are producing similar results but a careful examination and biometric testing of reported results show that this is not so. Since statistically significant differences can be demonstrated, it would seem essential that the details which led to such differences be carefully examined with the object of establishing wherever possible at least general principles which can be accepted. There are many difficulties which lie in the path which leads to such a goal; but one has only to look at the older figures from the League of Nations reporting clinics and to compare them with what is being achieved today to realize that enormous improvement has been made. The door is not closed to still further progress.

The present report deals with part of a larger study which has been going on since 1939. This report deals only with the results of therapy. The techniques and dosages which were chosen for the study are admittedly arbitrary and were applied after some preliminary exploration. There is no adequately based theory on which to determine the finer details although much interesting work has been done in this field. This is not the place to argue the theoretical advantages or disadvantages concerned. It was decided to apply deep x-ray daily except Sunday over as close to twenty-eight days as possible and to follow this immediately by the application of radium. Clinical experiments were run to determine the dosages of each which under these circumstances would be tolerated by the average patient. With minor variations, as individual study programs arose, this has been carried out on the whole group.

It was decided to deliver 3,000 tissue roentgens by x-ray diffusely to the whole pelvis including the tumor over as close to twenty-eight days as possible. Each patient is measured and, by the application of standard charts,

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tioners are asking if a smear cannot be taken to the exclusion of the idea that the basic and first step in the diagnosis of carcinoma is a proper examination of the patient. One is always impressed by the fact that in any series of cases where smear diagnosis is successful there are included a large number of patients in whom the tumor would have been recognized with ease had a routine pelvic examination been made.

There is another problem opened by a paper such as this on carcinoma in situ. Our experience has been that there is a great difference of opinion between pathologists as to whether the condition is present in any particular case. The findings of smear or biopsy are open to such a variety of interpretations. I think that Dr. Novak presented the most important feature of this difference of opinion when he drew attention to the fact that what has been called glandular invasion may be nothing more than metaplasia in relation to the cervical gland epithelium.

There is also the question as to what we are going to do with the patient when the diagnosis of carcinoma in situ has been made. It seems to me that total hysterectomy alone will allow the examination of sufficient tissue to determine the true significance of the condition. It is altogether likely, however, that time will prove that this procedure is not justifiable as the basis of proper treatment.

DR. YOUNGE (Closing).—Apparently I gave the wrong impression about our attitude toward the vaginal smear. I had hoped to make it clear that smears are 93 per cent accurate when carcinoma in situ becomes a lesion which is potentially dangerous, that is, with involvement of the cervical glands. We do use the vaginal smear and we do depend upon it.

In answer to the remark about serial block study of the entire cervix being necessary to rule out invasion, we have had in this group of cases eighty-three complete cervixes to study. In only two of these cases did we miss the diagnosis preoperatively of early invasion. Yet, the lesions were so small that a simple total hysterectomy was sufficient treatment. We know of a fair number of patients (at least thirty) who by mistake have had total hysterectomy without a suspicion of carcinoma being present. After the hysterectomy early invasive cancer was found; yet those patients are among the best follow-up results obtained by surgical treatment. Some may disagree with that statement, but I believe Dr. Meigs will back me up.

We do not really advocate cauterization of the cervix as the treatment for carcinoma in situ. Only one case was cauterized deliberately at her request in order to maintain her reproductive function. The twenty-three patients whose only treatment thus far has been cauterization have been followed most carefully, and we are certain that they are free of their disease at the present time. These cases unintentionally treated by cauterization and cured merely demonstrate that it can be done.

I somewhat disagree with Dr. Schwarz about biopsy versus conization. In our hands biopsy is accurate. We include a cervical curettage saving for the pathologist the blood clot as well as the tissue. No one at our hospital can conize a cervix and not get a high incidence of postoperative stenosis except Dr. Rock.

So far as breaking the news to the patient, it has been my responsibility to follow these patients. We insist that they have two or three positive biopsies at one- to two-month intervals before any treatment is done because in some of them the disease appears. It is explained to them that they have a condition about which pathologists disagree, but we personally feel that it may develop into cancer in the course of one to five years. It is explained to them that there is a long period of safety and that study is necessary in order to avoid an unnecessary hysterectomy. Our patients have been very cooperative and only a few have demanded treatment immediately. We are now following over thirty patients with anaplasia or questionable carcinoma in situ of the cervix. We do not want to do a hysterectomy on them at the present time because they are all young.

From our experience with carcinoma in situ of the cervix a radical hysterectomy is not necessary if the disease is evaluated carefully before operation.

patient will tolerate this and heal. A Kaplan colpostat is used in the vagina with as many portals to a maximum of three as the individual vagina will take. Radium in tandem is placed in the uterine cavity in an uncovered platinum container 5 to 6 cm. in length. One millimeter of platinum or its equivalent filtration is used. The vaginal colpostat has approximately 0.75 cm. of focal distance. When anatomically possible, two portals in tandem of 10 mg. of radium each are used in the uterus and three similar portals in the two arms and the central cork of the Kaplan colpostat in the vagina. Thus 50 mg. are applied for 100 hours. This dosage will vary somewhat with individual circumstances of the tumor and the patient. The dosage is of necessity decreased as the number of portals has to be decreased in the presence of vaginal shrinkage or absent uterus. The radium is applied on the day of the last x-ray treatment and is held in position by gauze moistened by an emulsion of 1 per cent neutral acriflavine to decrease bacterial growth.

The patients are hospitalized throughout the whole course of therapy. They are fed a high-protein, antianemic, low-residue, high-calorie diet. The usual studies are carried out to recognize abnormalities and usual treatment carried out for these when they occur.

The material consists of all patients who have come under control of the department from January, 1939, to the end of 1947. The League of Nations Cancer Committee rules have been applied and their staging used. Thus all patients with carcinoma of the cervix who have come to the gynecological department have been considered but those who had been treated previously for this condition are placed in a separate group referred to as nonreportable cases. A few patients have been excluded. Those who have been treated elsewhere and have come for follow-up are not included if they showed no tumor and so were not treated by this department. Almost all of the reportable cases had had no previous treatment. Two patients are included as reportable though a biopsy was taken elsewhere, a negligible quantity of radium applied, and the patients immediately referred. This was not considered as treatment elsewhere since it was not such as to be taken into any consideration in our own therapy and did not interfere for more than a few days with referral.

The patients with adenocarcinomas of the cervix are included since, surprisingly enough, they showed similar results to those with the squamous-cell tumors and so do not influence the conclusions. The three adenoma malignum cases all fall into the nonreportable group.

Every patient has been followed to death or to January, 1949. The department has been fortunate in the availability of funds to support a full-time trained secretary whose only duty is the organization of the follow-up of the gynecologic malignant disease patients. Multiple addresses of relatives and friends, preferably those who own property or are otherwise relatively geographically fixed, are taken on recognition of the tumor and this list is kept up to date. It is a simple procedure which has been of significant aid in an otherwise difficult and uncertain task.

The diagnosis has been made or confirmed by biopsy in every case. For all of those who have passed five years since treatment, the histologic material has been passed upon by the late Dr. Robert Meyer. There is no questionable carcinoma in the series.

A few patients have been treated by primary surgery for a variety of reasons. There were but seven of these and only two of them were treated more than five years ago. The results in these do not vary from the results in the general group sufficiently to change the rates. They are left in with the irradiation group for completeness.

the number and size of fields and the amount of irradiation given per treatment are determined. In preliminary studies, ionization chambers were placed in the craters of suitable tumors and the reality of the dosage determined. There is a very considerable variation between the calculated and the actual dose to the tumor area even under circumstances where accurate calculations are made. To guess what the tumor area gets from some arbitrary decision as to the dosage which is given to arbitrarily determined sizes of skin fields is a method so grossly inaccurate that it should not be used. It usually results in gross underdosage for purposes of medicolegal safety which is a poor basis for determination of dosage. In the earliest part of the study the tumor dosage often fell between 2,600 and 3,000 tissue roentgens because of fear of the larger dosage. Recently, as a separate study, the League of Nations Stage III tumors have been treated with a total of 3,500 tissue roentgens. There are not enough of either of these to influence significantly the end results.

During the time under consideration, relatively small changes in the roentgen therapy technique have been made. Between January, 1939, and June, 1942, the factors were: 220 kv., 1 mm. copper + 1 mm. aluminum filter, half value layer 1.7 mm. Copper; 60 and 70 cm. target-skin distance. Since June, 1942, the factors have been: 400 kv., .44 mm. tin + .25 mm. copper + 1 mm. aluminum filter, half value layer 3.9 mm. copper; 70 and 80 cm. target-skin distance.

As a rule, five fields were used: one anterior 18 by 20 cm., one posterior right oblique 14 by 18 cm., one posterior left oblique 14 by 18 cm., one right lateral 12 by 18 cm., and one left lateral 12 by 18 cm. One field was treated each day, 300 to 350 r./air. A total dose of 3,000 tissue roentgens was given to the center of pelvis in a period of 28 days. All these factors were, of course, varied somewhat to suit the individual. The only thing that was supposed to remain constant was the calculated dose of 3,000 tissue roentgens to the center. At first the dose was, however, somewhat lower and was gradually raised from a minimum of 2,500 to a routine of 3,000 tissue roentgens. An effort was made to limit the time to 28 days but a variation became necessary from about 25 to 35 days. Patients with large anterior-posterior and lateral diameters were given additional fields (perineal, anterior oblique fields). Two fields were sometimes treated the same day. Complications such as a drop in the patient's white blood count below 2,000, fever, or symptoms of uremia made it occasionally necessary to interrupt the treatments for a few days.

With 3,000 tissue roentgens to the center, a higher dose was obtained in certain portions of the pelvis and the maximum reached about 3,600 tissue roentgens.

The radium dosage, as in all other surface radium irradiation in the Department of Obstetrics and Gynecology, has been given over 100 hours. This is an arbitrarily chosen time with some vague theoretical advantages. But the standardization allows avoidance of one variable in the relationship between physical and biological dosage and so aids in accuracy. Multiple radium portals are used in order to get a maximum dose at as great a distance in the lymphatic drainage system as possible while still remaining within the tolerance of the local tissue which must be left so that it will heal. Compound isodose curves for an ideal setup show the cervical tumor itself to receive 15,000 to 25,000 gamma roentgens. This is more than is required and is not the determining factor in dosage. The cervix and vagina in the well-nourished

TABLE II. REPORTABLE CARCINOMA OF CERVIX UTERI, STAGE I. ABSOLUTE RESULTS

PATIENTS			SURVIVAL IN YEARS								
			1	2	3	4	5	6	7	8	9
1939	15	No.	15	15	15	15	15	14	13	12	12
		%	100	100	100	100	100	94	87	80	80
1940	16	No.	14	14	14	14	14	14	13	13	
		%	87	87	87	87	87	87	81	81	
1941	22	No.	21	18	15	15	15	14	14		
		%	95	82	68	68	68	64	64		
1942	28	No.	27	25	23	22	22	21			
		%	96	89	82	78	78	75			
1943	13	No.	12	11	10	10	10				
		%	92	85	77	77	77				
1944	12	No.	11	11	10	9					
		%	92	92	83	75					
1945	15	No.	15	13	13			Irradiation alone, 86			
		%	100	87	87						
1946	23	No.	18	16				Irradiation plus surgery,			
		%	78	70				8			
1947	36	No.	31								
		%	86								
Irradiation total			180	144	121	106	94	81	53	31	15
Survival			164	123	100	85	76	63	40	25	12
Absolute percentage			91	85	83	80	81.1	78	76	81	80
Surgery only			5	5	5	3	2	2	2	2	2
Survival			4	4	4	2	1	1	1	1	1
Total absolute			185	149	126	109	96	83	55	33	17
Survivals			168	127	104	87	77	64	41	26	13
Absolute cure rate			91	85	83	80	80.2	77	75	79	76

TABLE III. REPORTABLE CARCINOMA OF CERVIX UTERI, STAGE II. ABSOLUTE RESULTS

PATIENTS			SURVIVAL IN YEARS								
			1	2	3	4	5	6	7	8	9
1939	19	No.	18	14	11	10	10	10	10	10	
		%	95	74	58	53	53	53	53	53	53
1940	31	No.	25	21	17	17	17	17	16	16	
		%	81	68	55	55	55	55	52	52	
1941	26	No.	23	18	15	14	14	12	12		
		%	88	69	58	54	54	46	46		
1942	15	No.	13	10	10	10	9	8			
		%	87	67	67	67	60	53			
1943	18	No.	14	12	9	9	9				
		%	78	67	50	50	50				
1944	31	No.	25	21	18	17					
		%	81	68	58	55					
1945	29	No.	27	21	16			Irradiation only, 107			
		%	93	72	55						
1946	18	No.	14	12				Irradiation plus surgery, 2			
		%	77	67							
1947	27	No.	20								
		%	73								
Irradiation total			214	187	169	140	109	91	76	50	19
Survival			179	131	96	77	59	47	38	26	10
Absolute percentage			84	70	57	55	54.1	52	50	52	53
Surgery only			2	1	0						
Survival			2	1	0						
Total absolute			216	188							
Survivals			181	132							
Absolute cure rate			84	70							

In addition, there were eight patients who were treated more than five years ago by irradiation followed by surgery and two in whom the tumor was microscopic and found in the surgical specimens. These latter were irradiated after surgery. Five of these ten were alive and free of tumor at the end of five years. Since they, again, do not change the figure for the general material, they are included.

## Results

The results are shown in Tables I to V. The absolute five-year cure rate is 53.6 per cent (S.D.  $\pm$  2.8 per cent). For Stage I, this was 80.2 per cent (S.D.  $\pm$  4.0 per cent); for Stage II, 54.1 per cent (S.D.  $\pm$  4.8 per cent); for Stage III, 29.5 per cent (S.D.  $\pm$  5.2 per cent); and in Stage IV, a single patient of 16 survived. The standard deviations were determined on each year's survival figures. The proportions of the total material in each of these stages is shown at the bottom of the tables.

Two patients with Stage III tumors were not treated. One refused and one died with uremia and septicemia before treatment could be begun. Six patients with Stage IV tumors were not treated. Four of these had hopeless distant metastases and two died of intercurrent disease before treatment. All of these are included in the calculation of the absolute survival rate. All are dead. An attempt was made to treat all others but, for various reasons, a further 15 patients had therapy which was stopped before what could be considered adequate therapy had been delivered.

TABLE I. REPORTABLE CARCINOMA OF CERVIX UTERI, STAGES I-IV. ABSOLUTE RESULTS

PATIENTS			SURVIVAL IN YEARS								
			1	2	3	4	5	6	7	8	9
1939	52	No.	48	42	38	36	35	34	33	32	31
		%	92	81	73	69	67	65	63	61	60
1940	68	No.	47	40	36	36	34	34	32	32	
		%	69	59	53	53	50	50	47	47	
1941	72	No.	55	43	36	34	34	31	31		
		%	76	60	50	47	47	43	43		
1942	61	No.	49	42	39	37	35	33			
		%	80	69	64	60	57	54			
1943	44	No.	33	26	21	21	21				
		%	75	59	48	48	48				
1944	70	No.	53	43	37	35					
		%	76	61	53	50					
1945	71	No.	48	44	36						
		%	68	62	51						
1946	58	No.	42	34							
		%	72	59							
1947	81	No.	60								
		%	74								
Irradiation total			577	496	438	367	297	253	192	120	52
Survival			435	314	243	199	159	132	96	64	31
Absolute percentage			75	63	55	54	53.6	54	50	53	60
Surgery only			7	6	5	3	2	2	2	2	2
Survival			5	5	4	2	1	1	1	1	1
Total absolute			584	502	446	373	299	251	194	122	54
Survivals			440	319	247	201	160	133	97	65	32
Absolute cure rate			77	64	55	55	53.6	53	50	53	59
Patients seen 1939-1943							299				
Patients treated 1939-1943							291				
Relative cure rate							55%				



are roughly comparable to Stages I and II while the extensive tumors correspond to Stages III and IV.

#### NONREPORTABLE CARCINOMA OF THE CERVIX

		5 YEAR SURVIVAL, FREE OF TUMOR
"Local"	14 patients	8 or 57 per cent
"Extensive"	31 patients	3 or 9.7 per cent
Total	45 patients	11 or 24 per cent

#### Comment

The results of treatment of cervical carcinoma prior to 1939 have not been listed. As in other clinics, these show a steady improvement with no significant change in degree of clinical extension of the tumors over the years. Toward the end of this period about half the x-ray dosage and two-thirds of the radium dosage which has been given in the present study series were exhibited. The present study series shows a significantly greater cure rate. The cure rate reported here is significantly greater than that reported by a number of other investigators using different techniques but has been equaled by still others.

One would like answers to two questions. What are the significant features of the present techniques which have improved the results in our own material? What are the circumstances under which failure occurs and what next move might be made to recognize and attack these?

There is at present no simple answer to these questions. On the other hand, there can be no doubt but that gradual and steady improvement in end results is being made. The actual problem lies in what could be called the critical group of tumors or those which can be almost cured by a given technique. This involves a very few Stage I tumors but considerable numbers of Stages II and III. It is here that attention to detail and accuracy will yield a reward in producing the difference between ordinary and good results.

In this critical or borderline group, there can be little question but that accuracy of x-ray dosage to the tumor plays a significant role. The dosage which can be delivered to the tumor is limited by the tolerance of the intervening normal structures. It is only a fraction of that which has been experimentally determined as a so-called "tumor destructive dose." Because of the inevitable short focal distance of the vaginal and uterine radium application, and the inverse square of the distance law which limits the amount of irradiation energy delivered to depth, one is largely dependent on the x-ray with only a small contribution from the radium for the destruction of tumor at distance in the pelvic lymphatic system. Overdosage may destroy the patient directly, or, what amounts to the same thing, so interfere with normal tissue healing that its contribution in the final choking off of partially damaged tumor cells is interfered with and tumor recurrence results. Underdosage can lead to an occasional cure but the possibilities, particularly in this critical group, are not exhausted. Calculation of dosage, then, should start with the area at depth to be treated. Our studies have shown that a diffuse dose to the pelvis of 3,000 to 3,500 tissue roentgens over about 28 days represents the maximum reasonably safe dose. The dosage to skin, the sizes and numbers of fields, are calculated for each patient to supply this. This should also be the basis for reporting. The total amount of irradiation energy supplied to the skin is not a useful expression of the tumor dose. An accurate expression of depth dose is essential. If there be any doubt about the inaccuracy of the tumor dose which is based on a guess as to how many units should be given to the skin, the actual measurement of the dose which arrives at the cervical tumor is a simple undertaking and may prove surprising. It is true

TABLE IV. REPORTABLE CARCINOMA OF CERVIX UTERI, STAGE III. ABSOLUTE RESULTS

IRRADIATION ONLY PATIENTS			SURVIVAL IN YEARS								
			1	2	3	4	5	6	7	8	9
1939	17	No.	14	12	11	11	10	10	10	10	9
		%	82	71	65	65	59	59	59	59	53
1940	15	No.	7	4	4	4	2	2	2	2	
		%	47	27	27	27	13	13	13	13	
1941	23	No.	11	7	6	5	5	5	5		
		%	48	30	26	22	22	22	22		
1942	12	No.	7	6	6	5	4	4			
		%	58	50	50	42	33	33			
1943	11	No.	7	3	2	2	2				
		%	64	27	18	18	18				
1944	24	No.	16	11	8	8					
		%	67	46	33	33					
1945	21	No.	16	10	7						
		%	76	47	33						
1946	13	No.	9	5							
		%	69	38							
1947	13	No.	6								
		%	50								
Irradiation			149	136	123	102	78	67	55	32	17
Survival			93	58	46	35	23	21	17	12	9
Absolute percentage			62	43	38	34	29.5	31	31	38	53

TABLE V. REPORTABLE CARCINOMA OF CERVIX UTERI, STAGE IV. ABSOLUTE RESULTS

IRRADIATION ONLY PATIENTS			SURVIVAL IN YEARS								
			1	2	3	4	5	6	7	8	9
1939	1	No.	0	0	0	0	0	0	0	0	0
		%	0	0	0	0	0	0	0	0	0
1940	6	No.	1	1	1	1	1	1	1	1	
		%	16	16	16	16	16	16	16	16	
1941	1	No.	0	0	0	0	0	0	0		
		%	0	0	0	0	0	0	0		
1942	6	No.	2	1	0	0	0	0			
		%	33	16	0	0	0	0			
1943	2	No.	0	0	0	0	0				
		%	0	0	0	0	0				
1944	3	No.	1	0	0	0					
		%	33	0	0	0					
1945	6	No.	0	0	0						
		%	0	0	0						
1946	4	No.	1	1							
		%	25	25							
1947	5	No.	2								
		%	40								
Irradiation total			34	29	25	19	16	14	8	7	1
Survival			7	3	1	1	1	1	1	1	0
Absolute percentage			21	11	4	5	6	7	12	14	0

The individual types of tumor will be the subject of separate study but it might be worth noting here that considering only those who have passed the five-year interval since treatment, 52 per cent of 274 patients with squamous-cell tumors, 50 per cent of 10 with adenocarcinomas of the cervix, and 69 per cent of 13 with squamous-cell carcinomas of the cervical stump were alive and clinically free of tumor after this interval.

The patients with nonreportable tumors, or those who had been treated elsewhere prior to observation in the Department of Obstetrics and Gynecology of the University of Minnesota show little of interest. They are not grouped under the League of Nations four stages but those described as local tumors

impressed by the relationship between the size of the tumor and its local persistence after irradiation. The large extensive tumor may, on microscopic study, look the same as others before treatment and apparently respond similarly to the same dose of irradiation only to persist locally with an exasperating frequency. There is too much detail for presentation here but it might be pointed out that of the fifty patients with Stage III carcinomas of the cervix in this series who died as a result of the tumor, only five were known to have died with the pelvis free of tumor. There is a strong suggestion of some interference by the massive tumor with normal tissue healing ability. Control of this difficulty would be extremely valuable.

### Summary

1. Carcinoma of the cervix has been treated at the University of Minnesota Hospitals since the beginning of 1939 by means of daily x-ray therapy followed immediately by intravaginal and intrauterine radium. X-ray is given over as close to 28 days as possible and the details of this therapy are arranged so as to supply 3,000 tissue roentgens diffusely to the pelvis in this time. This is followed on the day of the last x-ray treatment by the insertion of radium which is left in place for 100 hours. Under ideal anatomical circumstances, two intrauterine portals in tandem and three vaginal portals in the Kaplan colpostat are used. Each contains 10 milligrams of radium for a total dosage of 5,000 milligram hours. This is decreased as the availability of space for these portals is decreased.

2. Every single patient has been followed to death or to Jan. 1, 1949. Every single patient has satisfactory biopsy control. There is no questionable carcinoma in the material.

3. The following results have been obtained on reportable material. The League of Nations classification is used.

Absolute five-year cure rate, 53.6 per cent (S.D.  $\pm$  2.8 per cent)  
Stage I, five-year cure rate, 80.2 per cent (S.D.  $\pm$  4.0 per cent)  
Stage II, five-year cure rate, 54.1 per cent (S.D.  $\pm$  4.8 per cent)  
Stage III, five-year cure rate, 29.5 per cent (S.D.  $\pm$  5.2 per cent)  
Stage IV, only 1 patient of 16 cured.

4. Adenocarcinomas, carcinomas of the cervical stump, and a few cases which were treated with surgery as well as x-ray are included. Because of their small number and the surprising similarity of the results with them to those of the general group of squamous-cell carcinomas, they do not influence the expression of results.

5. The techniques described have significantly improved the results previously obtained and are recommended.

The essential follow-up studies on which this report is based were only possible because of financial support generously made available by the Minnesota Division of the American Cancer Society, Inc.

### Discussion

DR. DANIEL MORTON, San Francisco, Calif.—The results which Dr. McKelvey has reported are excellent. Indeed, they are better than any that I know of. In attempting to account for the superiority of his figures one will naturally ask oneself certain questions.

that what is finally required is an expression of effect on the tumor or of biological dosage and that this is varied by many other considerations than dosage expressed in physical units alone. But unless this latter is as accurate as possible for the tumor-bearing area at depth under consideration, then all subsequent controls of accuracy fail. To interpret into a tumor dose the statement that 10,000 roentgens in air have been given to the skin produces a sense of frustration not unlike reaching out the window for the moon.

A similar word of warning should be said in regard to radium dosage. Again, the biological effect and not the physical dosage must be considered. Both normal tissue and tumor recover from the effects of appropriate amounts of irradiation energy. Unfortunately, there is reason to believe that the recovery of tumor from sublethal doses is more rapid than that of normal tissue. If this were the only factor concerned, the more rapid the delivery of a tolerated dose, the greater the advantageous differential of sensitivity might be expected to be. Clinical testing of this has led to the conclusion that there are other factors concerned and that something between single dose and infinitely prolonged therapy is desirable. It was somewhat arbitrarily decided to use for this study continuous therapy with about 28 days of x-ray followed immediately by 100 hours of radium application. The time factor is excluded as a variable from one patient to another. The results which it has produced are presented. They seem to have been significantly better than the reported results of some other types of time distribution and consequently are recommended. To prove that this is the most important feature of the results obtained is of course impossible.

The value of hospitalization throughout treatment is difficult to assess. It is expensive. But it allows the early recognition of sometimes dangerous disturbances. It has allowed treatment of the tumor to be driven through where considerations of safety would have demanded interruption in the outpatient. It has allowed dietary control, particularly of the protein intake, which may well be important, and which is now being studied. In general, it contributes to the accuracy of the handling.

In what direction should one turn for further improvement? It is obvious that surgery and irradiation must both eventually be supplanted by a more effective attack. In the meantime, the search must go on for methods of improving the effectiveness of the tools which are presently available. There can be no doubt but that accurately applied irradiation offers the most effective of such tools and that the surgical approach should be restricted to special circumstances. The problem now is to define objectively these special circumstances and some progress is being made here. It is hard to become concerned about the very early tumors since they can be effectively treated by either surgery or irradiation. Irradiation has consistently failed with the Stage IV tumors in spite of the fact that in a significant proportion of them, the host may be destroyed while the tumor is still apparently localized to non-vital though useful pelvic structures. Information as to the effectiveness of very radical surgery for these tumors must be obtained as soon as possible. Most gynecologists have satisfied themselves that this sort of procedure can be done with reasonable safety and not too much in the way of undesirable aftereffects.

The study of the material here reported makes it perfectly clear that the greatest single improvement may be expected to come from the solution to two problems. Some method must be found which will allow recognition at least by the time therapy is complete of those tumors which will fail to respond to irradiation. Histological studies on material taken on the day x-ray is completed and radium applied have been of questionable value in our hands. And, second, one cannot study such material as is presented here without being

care in securing adequate irradiation and in supervising the general health of his patients. All too often we are inclined to regard a patient who has carcinoma as "another case of cancer" and to neglect diet, the condition of the blood, etc. It is well known that anemic patients tolerate irradiation badly. Fat women with thick abdominal walls require more irradiation to the skin, to treat the cervix adequately, than do thin women. X-ray equipment must be standardized at regular intervals of at least every six months. These machines get out of order and deteriorate. As connections become less efficient and the tubes get older, the exposure time must be increased in order to deliver the same dosage as when the equipment was new. In the case of radium filtration, the distance between the radium tube and the lesion being treated must be taken into consideration as well as the time during which the radium is applied.

DR. KARL WILSON, Rochester, N. Y.—I would like to see a little more attention paid to the selection of radioresistant tumors, and that is a difficult thing to do. The histology is not the entire picture. You take a biopsy and you think the tumor is radiosensitive. You treat that patient by irradiation therapy and the result is not what you want so you say it was radioresistant.

It has been our custom for the last year in the follow-up of treated patients to take repeated vaginal smears again and in general we find that when a patient has been successfully treated, the smear quickly becomes negative. On this basis I am not prepared to make a positive statement but I suspect that if, eight weeks after irradiation therapy has been completed, we can still demonstrate cancer cells, we regard it as radioresistant, and that may be the group of patients who may be suitable for surgical treatment of their carcinoma in Stage I or II cases.

DR. WILLIAM P. HEALY, New York, N. Y.—This report is most stimulating, at least to us who carry out irradiation therapy in the treatment of carcinoma of the cervix. Dr. McKelvey has presented the best end results we have heard of. I was very much interested and pleased with the point he makes of preliminary roentgen irradiation. This is carried out in his cases first and is finished before radium is applied. At the Memorial Hospital we brought that out many years ago. We emphasized also the importance and value of biopsies taken at intervals during the course of roentgen therapy to show the regressive effect of such treatment on the tumor. I was interested in the fact that on the last day of roentgen therapy they start radium therapy. We have found it desirable with a similar amount of roentgen therapy to delay the radium application about ten days.

Dr. McKelvey emphasized that adenocarcinoma and squamous carcinoma of the cervix respond in a similar way to irradiation therapy. We have found that this is true: that there is no difference whatsoever in response of adenocarcinoma or squamous carcinoma; that the response depended entirely upon the clinical classification of the case and not on the histologic structure of the tumor.

I think that possibly one of the most important factors in his excellent end results is the fact that his patients are hospitalized throughout their term of therapy. That must be a very important item in leading to better end results. We could not do that for the same reasons stated by Dr. Morton, but I do think that having the patient under the observation of one competent person or a team of two or three competent men throughout the course of therapy and under close observation after hospitalization will increase the percentage of favorable results.

DR. LEWIS C. SCHEFFEY, Philadelphia, Pa.—I shall only emphasize one phase and that is the use of preliminary x-ray irradiation. At the Jefferson Clinic we have found, after we had gotten away from the hit-or-miss use of radium and x-ray interchangeably, in the series which we could evaluate most recently on the basis of adequate x-ray irradiation, that our over-all results had increased from 25 to 38 per cent, in spite of the fact that our Stage I and II cases together are in the neighborhood of only 12 per cent. We also can evaluate on a five-year basis a series of cases in which both external and transvaginal irradiation was used as a preliminary to radium and this group has shown no increase in salvage results with respect to the addition of the transvaginal route.

First, are there features of the treatment technique itself which set it apart from others and to which one may attribute an improved response? Second, are there other factors inherent in the material which might be responsible? In answer to the first question, Dr. McKelvey has pointed out that certain features of the treatment and general management of the patients have been fairly constant, and therefore deserve attention as possible contributors to the excellence of the results. I refer to (1) the fixed plan of irradiation, involving as it did a set dose of both x-ray and radium given over exactly the same length of time in each individual case, and (2) hospitalization during the entire treatment, allowing for careful observation, prompt treatment of anemia, infection, etc., and proper nutrition. I am not certain that a fixed plan of irradiation is actually superior to one involving some individualization, provided that the individualization is administered by one who thoroughly understands the problem. However, the fixed plan which was followed seems to have been a happy one, involving reasonably adequate doses of both x-ray and radium, in favorable proportions. Since the fixity in the time element was the most constant and outstanding feature of the irradiation we cannot fail to recognize its possible importance. Hospitalization during treatment is of definite value, I am sure. The biggest drawback to such a plan in most institutions and for most individuals is the expense, not only in money, but in bed space. Nevertheless, I believe that the results at Minnesota are sufficiently outstanding to stimulate more adherence to such a plan.

With regard to the second question, I should like to exhibit the following table which compares material and results from the Minnesota Clinic with those from the University of California Clinic, and the composite figures in the last (collated in 1939) Annual Report of the League of Nations Health Organization.

CASES							FIVE-YEAR SURVIVALS		
INCIDENCE OF THE VARIOUS STAGES							IN PER CENT		
STAGE	MINN.		CALIF.		L. OF N.		MINN.	CALIF.	L. OF N.
	NO.	%	NO.	%	NO.	%			
I	94	(31.6)	114	(20.5)	1,280	(11.6)	81.1	65	56.1
II	109	(36.6)	197	(35.8)	3,054	(27.8)	54.1	48	37.3
III	78	(26.3)	177	(31.9)	4,414	(40.2)	29.5	24	22
IV	16	(5.4)	67	(11.8)	2,220	(20.2)	6	4.4	4.4
	297		555		10,970		53.6	39.9	26.7

It is obvious that the group of cases reported by Dr. McKelvey contains a much lower proportion of advanced cases (Stages III and IV) than do either of the other two series. This in itself will inevitably make a considerable difference in the final salvage in favor of the Minnesota series. In turn, the University of California material is better than that represented by the composite figures, and in turn the five-year salvage is considerably better. Perhaps there have been differences in interpretation of what constitutes the various stages of advancement; however, such differences could hardly account for the vast differences in the figures. I would like to believe that education is responsible for more and more earlier diagnoses. If this is true then we must compliment Minnesota for being so outstanding in this respect.

Another point of interest in the comparison is that Dr. McKelvey's results are also superior in the individual stages. This may be due to actual superiority in the technique of treatment, as discussed previously. It is not entirely understandable, however, since the greatest superiority is noted in the early stages, especially Stage I, in which differences in technique should have the least effect. I would like to suggest that Minnesota women may be more responsive to irradiation than some others. This is not meant to be facetious since vast differences in tissue and tumor susceptibilities to irradiation, due to unknown factors, have long been recognized.

It is my belief, then, that the superiority of the results reported should be attributed not only to the technique and management employed, but also to other factors which relate specifically to the type of material involved, and possibly to other unknown factors.

DR. CHARLES A. BEHNEY, Philadelphia, Pa.—Dr. McKelvey's paper gave me the impression that perhaps his better results may have, at least in part, been due to his extreme

## FURTHER STUDIES ON THE EFFECT OF IRRADIATION THERAPY FOR CARCINOMA OF THE CERVIX UPON THE URINARY TRACT\*

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**I**N 1939 we reported our observations upon the effects of carcinoma of the cervix and its treatment upon the urinary tract. In that study we had attempted to examine urologically patients subjected to irradiation therapy for carcinoma of the cervix before the institution of treatment and at various intervals after completion of therapy. Forty-six patients were so studied before treatment, and the conclusion drawn from that study was that evidence of ureteral obstruction before the institution of treatment constituted an extremely grave prognostic sign.

Since some of the patients studied before treatment died before sufficient time had elapsed to make posttreatment studies worth while, and as others failed to cooperate, only 33 patients were studied urologically subsequent to completion of irradiation therapy. Of these, 16, or 48.4 per cent, showed some evidence of ureteral obstruction and 18, or 54.5 per cent, some type of bladder lesion. In only about 15 per cent, however, were the ureteral obstructions sufficiently severe to be of clinical importance, and in only 20 per cent were the bladder lesions of serious clinical significance.

At the time of this report less than five years had elapsed in most of the patients since the irradiation therapy had been administered, but as they appeared to be clinically well of carcinoma it was assumed that the effects observed upon the urinary tracts were the result of irradiation damage rather than of persistent or advancing carcinoma. We have felt that it is now worth while to restudy and re-evaluate this group of cases to determine to what extent we were right in assuming freedom from carcinoma and therefore assigning the urological lesions to irradiation damage. In the course of this restudy we have found that one patient originally designated as exhibiting only a mild bladder reaction has subsequently developed very dense ureteral strictures, and another patient, who at the time of the original report showed no urological lesions, as late as 1946 developed vesicovaginal and rectovaginal fistulas and complete occlusion of one ureter with large hydroureteronephrosis on the opposite side (Fig. 1).

\*Presented at the Seventy-Second Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 16 to 18, 1949.

DR. JOSEPH BAER, Chicago, Ill.—Will the speaker evaluate what continuous hospitalization does which cannot be done on an ambulatory basis with a carefully observed record?

DR. McKELVEY (Closing).—It is impossible to be certain of the significance of any one specific factor. This study was designed to test a given set of circumstances. I do not know why there are so many early cases in this material but I think I know one reason. I am satisfied that in those Departments of Gynecology where the histology on material obtained from the clinic is checked by a gynecologist there is an increase in the number of early cases found. More of the tissue is likely to be examined. The material presented today passed through both the Departments of Gynecology and Pathology and separate reports were placed on the record. There are some tumors which have been found by smear but none of this material appears in this five-year cure group.

There is no question but that meticulous care of the patient and of the irradiation details pays off. It appears that the amount and time distribution of dosage play a part but it is impossible to prove it.

Dr. Wilson put his finger on one important problem. How can we recognize those tumors that will be radioresistant? The histologic study of the tumor immediately after x-ray therapy is completed has not proved accurate in our hands. It would be of enormous value to be able to recognize early those tumors which will recur locally. No accurate method is presently available. A study on the effect of protein feeding is now under way. We know what part protein plays in major surgery and perhaps it does the same here too. Local recurrence of tumor may well be due to a deficiency of normal tissue response rather than tumor resistance to irradiation energy. The adequacy of normal tissue nourishment could be very important itself.

Follow-up smear study has been useful. It will recommend itself to all who have attempted to deal with biopsy material from patients who have been irradiated. The difficulty of obtaining adequate biopsy material and often of interpreting it is common knowledge.

Dr. Baer has asked for an evaluation of continuous hospitalization for these patients. In answering this, it should be pointed out that the dosage which was used was clinically determined. There is considerable experience with lower dosages and the older material at the University of Minnesota Hospitals was used for this control. Larger dosages than those here reported have been used by the author experimentally. These produced too frequent damage. The conclusion was that even the massive dosage used on the patients reported here produced on occasion sufficiently serious disturbances to require hospitalization for early recognition and treatment. It was twice the dosage previously used and, frankly, we are afraid to give it without detailed observation. There are many patients in whom, because of their specific circumstances, one would not dare to continue massive therapy without close observation. It appears to be very important to avoid interruption of the course of therapy, and hospitalization has helped in accomplishing this. Agranulocytic leucopenia is of sufficiently frequent occurrence to justify hospitalization. Those who have seen these patients die of leucopenia will agree that daily determination of white blood cell counts under exactly similar circumstances is necessary. It is difficult to interpret white counts taken at any time of the day.

It is hard to avoid being convinced that diet plays a part, probably in maintenance of normal tissue response to the tumor area. All have seen the cachectic patient with a great tumor that can be blown out with irradiation therapy but which simply continues to grow from the margin. Local tissue reaction is important and the dosage given must be kept under the amount which results in destruction of normal tissue. But local tissue nourishment is probably equally important. Have you tried to force food into these patients? It cannot be done adequately at home but can be accomplished by trained hospital staffs. It is astonishing to realize how much can be done by explaining these things to the patient.

It is admitted that this has been an expensive form of therapy but in our experience it has paid off by comparison with other techniques used. There are better bases than cost on which to determine the details of malignant disease therapy.



TABLE I. PRESENT STATUS OF CASES SHOWING UROLOGICAL LESIONS FOLLOWING IRRADIATION FOR CARCINOMA OF THE CERVIX, REPORTED IN 1939

LOCATION OF LESIONS	TOTAL PA- TIENTS	BLADDER LESIONS		URETERAL OBSTRUCTION		PRESENT STATUS		
		SE- VERE	MILD	SE- VERE	MILD	LIVING	DEAD	LOST
Bladder lesions only or no lesion	7	3	3 (1 no lesion)	0	0	6	0	1
Ureteral obstruction only	6	0	0	2	4	1	2	3
Bladder lesions and ureteral obstruction	10	5	5	6	4	5	5	0
Total	23	8	8	8	8	12	7	4

- Notes: 1. One living patient has recurrent carcinoma in right iliac lymph nodes after 11½ years.  
 2. The 4 lost patients are assumed to be dead of carcinoma.  
 3. Five of the dead patients are either known or assumed to be dead of carcinoma.  
 4. Two of the dead patients were proved by autopsy to have had no residual carcinoma (Fig. 2).  
 5. These two plus eleven living patients free of carcinoma make 13 patients available for the present analysis.

TABLE II. LESIONS PRESENTLY EXISTING OR EXISTING AT TIME OF DEATH IN THE THIRTEEN CASES AVAILABLE FOR PRESENT ANALYSIS

Vesicovaginal fistula	4 (2 with rectovaginal fistula)
Complete occlusion of one ureter with functionless kidney	3 (2 of these are in patients with vesicovaginal fistula)
Ureteral stricture with marked hydro-ureteronephrosis	2
Ureteral stricture with slight or moderate hydronephrosis	4
No lesions (original mild bladder lesions only)	4

Since 1940 our standard technique for irradiation of carcinoma of the cervix has been the application of two doses of radium of 2,400 mg. hr. each with an interval of two weeks between the two applications, for a total of 4,800 mg. hr. An occasional patient has been given 4,000 mg. hr. in a single dose. For each application 100 mg. of radium element are used. A rubber tube containing two 25 mg. radium capsules in tandem is placed in the cervical canal, and a linen plaque containing 50 mg. of radium is placed against the cervix. The type and arrangement of the radium tubes in the plaque depends on the size of the cervix. The filtration has varied between 0.5 and 1.5 mm. of platinum plus 1 to 3 mm. of rubber for that in the intracervical tandem. The vagina is always packed very tightly and carefully to hold the plaque in place and to remove the bladder and rectum as far as possible from the radium. The bladder is kept constantly empty by means of a retention catheter as long as the radium is in place.

Except for the hopelessly advanced group who are treated palliatively with deep x-ray therapy only, all of the patients have received a combination of radium and roentgen irradiation. For the x-ray therapy two anterior abdominal and two posterior fields measuring 15 by 15 cm. are used. Because of danger of damage to the head of the femur we have never used lateral fields. Prior to 1941 all cases were treated at 200 KVP. At each treatment 200 r. measured in air were given over each of two fields, and the treatments were administered three times a week until a total of 8,000 r. measured with backscatter,

For this study we have divided the patients into three groups according to the location and nature of the original lesions (Table I). From this table it will be seen that there were 13 patients in whom the evidence is practically incontestable that the carcinoma was cured.



Fig. 1.



Fig. 2.

Fig. 1.—E. M. (Case 118897), treated for Stage II carcinoma of cervical stump in July and August, 1937. In 1939 the patient was apparently well and showed no evidence of urological complications. In 1946 she developed a large vesicovaginal fistula with complete occlusion of the right ureter. The pyelogram made March 24, 1947, shows evidence of stenosis of the left ureter in the intravesical portion. The patient has been treated by repeated dilatations of this stenosis.

Fig. 2.—C. Z. (Case 127093). Thirty-three minute intravenous pyelogram made three years after treatment with 2,600 mc. hr. of radium emanations for supposed Stage III carcinoma. At the time of this examination the patient had been suffering for more than a year from an intense ulcerative cystitis with encrustations. The films taken earlier than thirty-three minutes showed little visualization. (From Everett, H. S.: *Am. J. Obst. & Gynec.* 38: 889, 1939.) Subsequent to this report this patient developed vesicovaginal and rectovaginal fistulas. She died of uremia fifty-seven months after treatment and autopsy revealed no remaining carcinoma.

The present or ultimate status of the urinary tracts in these 13 patients is shown in Table II.

Shortly after the completion of the study reported in 1939, the technique of irradiation therapy, especially that of radium administration in our clinic, underwent a radical change. The patients included in the 1939 report had been treated as ambulatory patients with the rapid administration of irradiation using large quantities of radon. The total dosage administered to each patient varied considerably, but in nearly all cases was considerably less than that which we are giving now. An average dose was 3,000 mc. hr. administered by the use of 3 gm. equivalents of radon for a period of one hour. Many of the patients with early lesions received no x-ray therapy. The exact dosages received by all patients ultimately showing evidence of urinary tract damage are contained in the tables in the 1939 report.



Fig. 3.

FIG. 3.—E. R. (Case 240433), Stage II carcinoma. Intravenous pyelograms made Sept. 2, 1942, before the institution of treatment, showing normal upper urinary tracts.



Fig. 4.

FIG. 4.—Left retrograde pyelogram made May 9, 1947, of the same patient as illustrated in Fig. 3. Note the large hydronephrosis. The left kidney was functionless and left nephroureterectomy was considered. Before this could be arranged, however, further evidence of recurrent carcinoma in the left iliac lymph nodes developed and the patient has since succumbed to carcinoma.

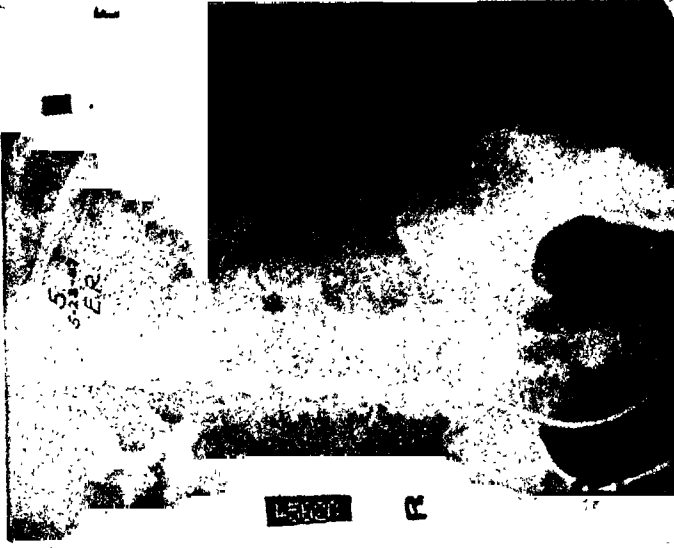


Fig. 5.

FIG. 5.—Right retrograde pyelogram made May 23, 1947, of the same patient illustrated in Figs. 3 and 4. There is some dilatation as compared with the pretreatment pyelograms.

or 2,000 r. to each field, had been given. The factors were a skin-target distance of 50 cm., and a Thoraeus filter equivalent to 2 mm. of copper plus 1 mm. of aluminum. The half value layer was 1.9 mm. of copper.

Since 1941 most of the patients have been treated at 400 KVP., with 250 r. being administered to each of two fields three times a week until a total of 10,000 r. measured with backscatter, 2,500 r. to each of four fields, has been administered. The S. T. distance has been increased to 70 cm. and a Thoraeus filter equivalent to 3 mm. of copper plus 1 mm. of aluminum is used. The half value layer is 5 mm. of copper.

In those cases with Stages I or II carcinoma the radium is administered first and the roentgen therapy is started two weeks after the second radium treatment. In the more advanced cases the x-ray treatments are administered first and followed by radium therapy as described, if there has been a satisfactory response to the roentgen therapy.

For the sake of comparison, we wish now to present the findings on urological study of those patients treated during the years 1940 to 1942, inclusive, who survived for five years or more subsequent to their initial treatment. The absolute five-year survival rate for these three years has been 26 per cent. The results of these studies are shown in Tables III, IV, and V, and may be summarized as follows:

TABLE III. NUMBER OF PATIENTS TREATED IN 1940-1942, INCLUSIVE, WHO HAVE SURVIVED 5 YEARS OR MORE, SHOWING RESULTS OF PRETREATMENT UROLOGICAL STUDIES, AND THE LATE RECURRENCE OF CARCINOMA

STAGE OF CARCINOMA	NUMBER SURVIVING	NUMBER WITH PRETREATMENT UROLOGICAL STUDIES	CONDITION OF URINARY TRACT			LATE RECURRENCE AFTER 5 YEARS
			NORMAL	DILATATION		
				UNILAT.	BILAT.	
I	24	15	8	6	1	2
II	9	5	5			2
III	10	6	3	3		1
Total	43	26	16	9	1	5

TABLE IV. POSTTREATMENT UROLOGICAL STUDY OF PATIENTS TREATED 1940-1942, INCLUSIVE, AND SURVIVING MORE THAN 5 YEARS, WHO HAD BEEN SUBJECTED TO UROLOGICAL EXAMINATION BEFORE TREATMENT

STAGE OF CARCINOMA	CONDITION OF UPPER URINARY TRACTS BEFORE AND AFTER TREATMENT			
	NORMAL BEFORE AND AFTER	DILATATION BEFORE AND AFTER	DILATATION AFTER ONLY	NORMAL AFTER ONLY
I	3	5	0	
II	1	1	1	
III	2	1	Late recurrence	1
Total	6	7	1	1

TABLE V. POSTTREATMENT STUDY OF 7 PATIENTS TREATED IN 1940-1942, INCLUSIVE, WHO HAD NOT BEEN STUDIED UROLOGICALLY BEFORE TREATMENT

STAGE OF CARCINOMA	CONDITION OF URINARY TRACT		
	NORMAL	DILATATION	
		UNILAT.	BILAT.
I	2	2	
II	2	1	
III			
Total	4	3	0

No bladder ulcerations or vesicovaginal fistulas have *as yet* occurred in any of these patients. We say *as yet* because, even though six to eight years have elapsed since treatment in all of them, we have seen such bladder lesions develop as late as twelve years subsequent to treatment. Of the total group of 149 patients treated in the three years under consideration, 10, or 6 per cent, developed vesicovaginal fistulas. None of these 10, however, survived as long as five years, and all of them are assumed to have died of carcinoma.

In this group, then, we have found no urological lesions that can be conclusively attributed to irradiation therapy. We must conclude, therefore, that the technique and methods of administration of the irradiation therapy used during the years under consideration were far superior to those previously used in so far as the prevention of postirradiation urological complications is concerned.



Fig. 8.



Fig. 9.

Fig. 8.—A. M. (Case 234772), Stage I carcinoma. Right pyelogram June 2, 1942, eight months after treatment showing hydronephrosis apparently due to ureteropelvic junction obstruction.

Fig. 9.—Intravenous pyelogram Dec. 17, 1947, of the same patient illustrated in Fig. 8. There has been progression of the hydronephrosis, but it is producing no symptoms and the patient is apparently well of carcinoma. Obstruction in this region could hardly result either from the carcinoma or its treatment.

During the war years due to shortage of personnel and more particularly to the frequent almost complete unavailability of x-ray films for use except in the most urgent cases, the routine urological study of cases with cervical carcinoma was discontinued. The patients treated, therefore, during those years will never be available for accurate statistical analysis as regards urological damage. Since the war, however, the routine urological studies have been resumed, but sufficient time has not elapsed to permit a study of these patients to be of any statistical value.

Since 1945 we have treated a small series of 39 cases with somewhat larger doses of radium. This second technique differs from the one described above in that the lower 25 mg. tube in the intracervical tandem is replaced by

Forty-one patients survived more than five years after their original treatment. Twenty-six of these were studied urologically before treatment (Table III). In 16 the urinary tracts were normal. In 10 there was evidence of slight ureteral stricture with slight hydroureteronephrosis which in all but one was unilateral. Twenty-two patients have been studied urologically since treatment, and with two exceptions these studies have been made more than five years since treatment. Fifteen of these were from the group studied before treatment (Table IV). In 13 there was no essential change in the urinary tracts between the pretreatment and posttreatment studies, six being normal and seven showing mild unilateral hydroureteronephrosis in both studies. One patient whose upper urinary tracts were normal before treatment showed a large functionless left hydronephrosis seventy-two months later (Figs. 3, 4, and 5) but has subsequently developed further evidence of a late recurrence in the left iliac lymph nodes. The ureteral obstruction in this patient was the first evidence suggesting possible recurrence. Another patient with original Stage III carcinoma and a moderate left hydroureteronephrosis now shows an essentially normal urinary tract on that side (Figs. 6 and 7).



Fig. 6.

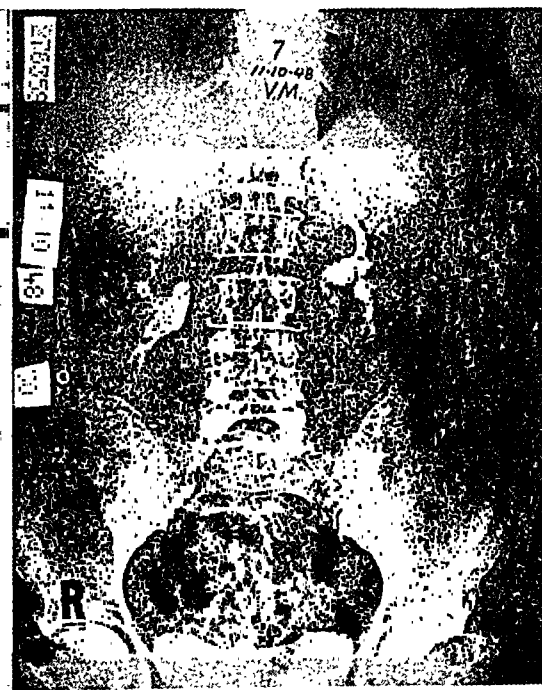


Fig. 7.

Fig. 6.—V. M. (Case 276359), Stage III carcinoma. Pretreatment intravenous pyelogram Nov. 13, 1942, showing moderate left hydronephrosis.

Fig. 7.—Intravenous pyelogram Nov. 10, 1948, of the same patient illustrated in Fig. 6. The patient has been clinically well of carcinoma for more than six years, and there has been complete regression of the left hydronephrosis.

Seven of the patients studied subsequent to treatment had not been subjected to pretreatment studies (Table V). In four of these the urinary tracts are normal. In one there is slight right hydronephrosis. In one with a late recurrence in the right iliac lymph nodes there is a functionless right kidney. The third patient has a large right hydronephrosis which has progressed since it was first discovered eight months after treatment, but which is apparently due to ureteropelvic junction obstruction and therefore is not related to the carcinoma or its treatment (Figs. 8 and 9).

could be attributed at least partly to the radiation therapy. It is felt that the majority of these patients showing radiation reaction at the present time will eventually have a good postradiation result, it being too soon after treatment to be sure of the final response to therapy. However, two of these patients, including one of those who died, sustained severe damage to the urinary tract, which we feel should be mentioned in this report.

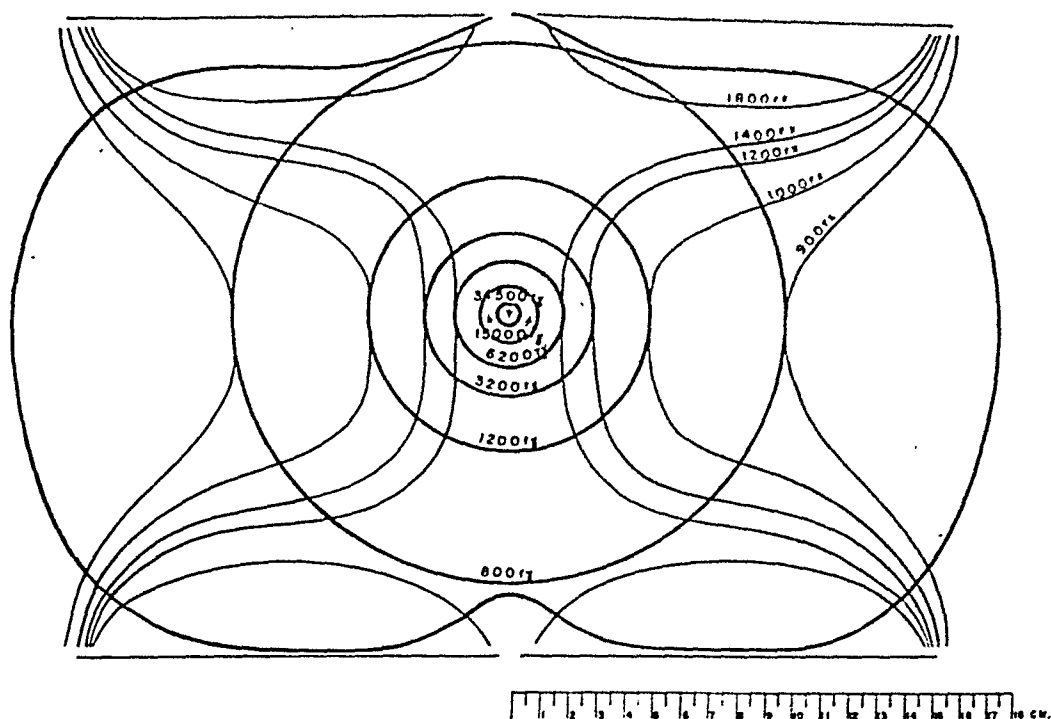


Fig. 11.—Shows the distribution of intensity of irradiation from x-ray and radium for the following conditions: The x-rays are delivered in 200 r. doses measured in air through two posterior and two anterior pelvic fields 15 by 15 cm., each field receiving a total of 2,000 r. The factors are 200 KVP., 50 cm. skin-target distance, Thoracis filter equivalent to 2 mm. of copper plus 1 mm. of aluminum. The radium is administered in one intracervical tandem preparation and one contracervical plaque. The first contains two 25 mg. tubes with a wall thickness of 1 mm. of platinum and 3 mm. of rubber. The second consists of five 10 mg. tubes with a wall thickness of 0.5 mm. of platinum. Two applications are administered, each consisting of 1,200 mg. hr. of intracervical and 1,200 mg. hr. of contracervical radiation.

This is the technique used in 1940 and the earlier part of 1941. Later in 1941 and in 1942 the radium technique was the same but the x-ray dosage was that shown in Fig. 10. The five-year survivors among the patients treated in these years have shown no urological damage attributable to irradiation.

CASE 1.—A 25-year-old Negro, para ii, complained of periodic intermenstrual bleeding of one year's duration. One month before coming to the clinic she bled continuously for ten days. Lower abdominal pain had been present for five months. Examination revealed a deeply lacerated cervix with a hypertrophied anterior lip, and a granular lesion measuring 2 cm. on the left side of the cervix. The fundus was normal and was free, but there was induration in the medial part of the left parametrium. A biopsy was reported "Epidermoid Carcinoma of the Cervix, Transitional Cell Type," and a diagnosis of carcinoma of the cervix, clinical Stage II was made. The patient was given two radium treatments of 3,000 mg. hr. each at two-week intervals, and this was followed by the usual course of 10,000 r. of deep x-ray therapy at 400 KVP. Five months after treatment was started a small ulcer was noted on the cervix, and the parametrium on both sides were found to be quite indurated. A month later she developed persistent rectal bleeding and anemia requiring blood transfusions, and eight months after treatment was started she was found to have a rectovaginal fistula. In order to put the bowel at rest a colostomy was done

a 50 mg. tube, making a total of 75 mg. of radium applied to the cervical canal. The same type of 50 mg. contracervical plaques described above are used, so that, in all, 125 mg. of radium are applied for two applications of 3,000 mg. hr. each. The filtration has varied between 0.5 and 1.5 mm. of platinum, plus 1 to 3 mm. of rubber in the case of the intracervical tandem. The x-ray dosage and technique in this group have been the same as that described for the former group after 1941, that is, a total of 10,000 r. measured with backscatter, administered from a 400 KVP machine. The isodose curves for this technique are shown in Fig. 10, and may be compared with those for the original technique of 4,800 mg. hr. of radium and 8,000 r. of x-ray from a 200 KVP machine shown in Fig. 11.

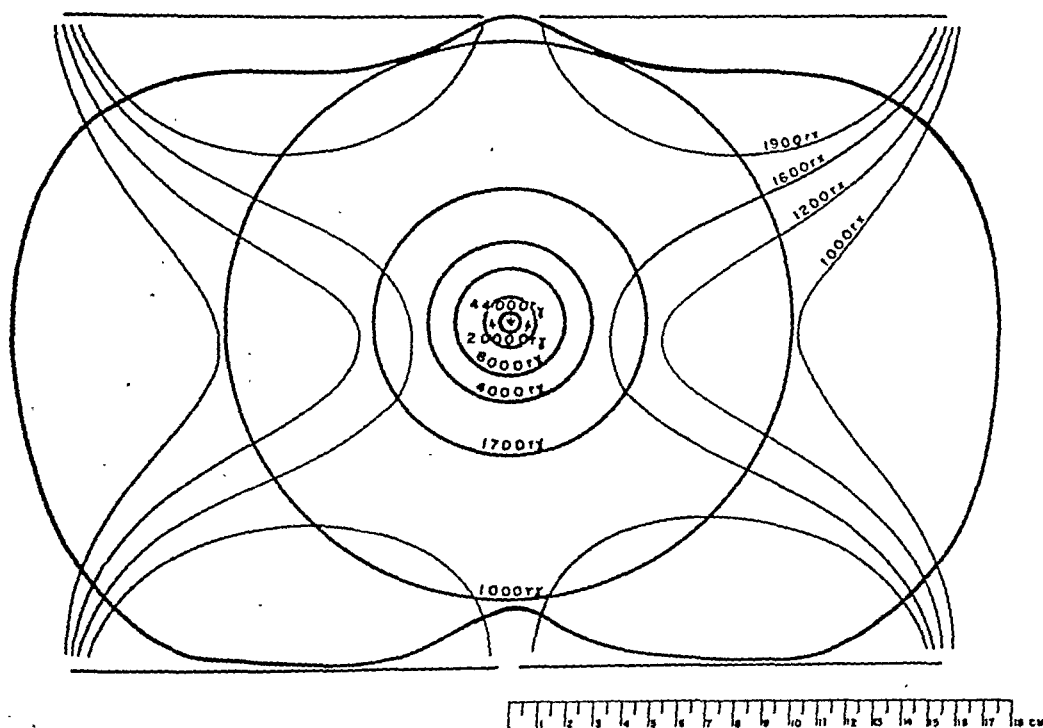


Fig. 10.—Shows the distribution of intensity of irradiation from x-ray and radium for the following conditions: The x-rays are delivered in 250 r. doses measured with backscatter through two posterior and two anterior pelvic fields 15 by 15 cm., each field receiving a total of 2,500 r. The factors are 400 KVP., 70 cm. skin-target distance, Thoraeus filter equivalent to 3 mm. of copper plus 1 mm. of aluminum. The radium is administered in one intracervical tandem preparation and one contracervical plaque. The former contains one 25 mg. and one 50 mg. radium capsule with a wall thickness of 0.5 mm. of platinum and 3 mm. of rubber. The plaque consists of five 10 mg. tubes with a wall thickness of 0.5 mm. of platinum. Two applications are administered, each consisting of 1,800 mg. hr. of intracervical and 1,200 mg. hr. of contracervical radiation. This is the technique which was used in the thirty-nine patients who showed a high percentage of severe irradiation reactions.

In both this chart and Fig. 11 the intensity of radium irradiation is shown by the heavier concentric circles, and that of x-rays by the lighter curves. The intensity of radium irradiation is expressed in r., and the depth doses from x-radiation, expressed in r., represent percentage values derived from the total dosage, which are expressed in r. measured in air.

In the group of cases treated with the smaller radium dosage (4,800 mg. hr.), the incidence of radiation necrosis of the cervix severe enough to cause apprehension has been approximately 4 per cent of the cases treated. In the 39 cases treated with 6,000 mg. hr. of radium, 12 cases showed moderate to severe radiation necrosis of the cervix or other reaction such as induration in the parametrium or cul-de-sac, an incidence of 31 per cent. Thus an increase in the total radium dosage from 4,800 to 6,000 mg. hr. resulted in an increase in pelvic irradiation reactions from 4 to 31 per cent, with two deaths which



felt in this case that surgery was contraindicated because of the medical complications, and irradiation therapy was used in its place.

On Oct. 28, 1947, a sharp conization of the cervix was done in order to supply additional tissue for microscopic examination. Study of this tissue revealed an early invasive carcinoma of the cervix, of basal-cell type. Immediately after the conization the patient was given 1,837 mg. hr. of intracervical radium therapy with one 25 and one 50 mg. radium capsule in tandem in a rubber cot. Next day 1,225 mg. hr. were given contracervically, and two weeks later 1,800 mg. hr. were given intracervically and 1,200 contracervically using the same technique. Between Dec. 2, 1947, and Jan. 28, 1948, the patient was given a total of 10,000 r. of deep x-ray therapy over four pelvic portals. The patient was well for six weeks when she returned complaining of abdominal pain on urination, and pelvic examination revealed induration and fixation in the left parametrium. Three months after treatment was completed she had a sudden profuse vaginal hemorrhage and was admitted to the hospital. On examination there was a large irradiation ulcer replacing the cervix, and a large vesicovaginal fistula measuring 3 to 4 cm. in diameter. Profuse bleeding continued from the edges of the ulcer in spite of continued packing with Gelfoam gauze, and it was finally necessary to ligate the anterior branches of both hypogastric arteries in order to control the hemorrhage. It was discovered at operation that there was a moderate right hydroureter, and the right ureter was transplanted to the sigmoid colon to preserve the function of the right kidney. Since operation the patient has done well except for an episode of vaginal bleeding from the border of the vesicovaginal fistula in October, 1948. It has been decided to transplant the left ureter to the colon eventually, but this procedure has been postponed because it is feared that the anesthesia may influence adversely the course of the pulmonary tuberculosis, which is doing well at the present time.

We feel that the extensive damage to the urinary tract as well as to some of the other pelvic structures in this case is due as much to the fact that radium was applied immediately after the conization of the cervix as to the large dose of radium that was used. We have since discontinued both of these procedures.

### Comment

The main objective of irradiation therapy of carcinoma of the cervix should be, and no doubt is, to obtain as high a salvage rate as possible, and at the same time to avoid inflicting serious damage upon normal tissues. The purpose of a study of this type is to try to determine if possible what factors of technique of irradiation therapy are most likely to achieve this objective. From this study and others gathered from the literature, it would seem that, of the two components of the treatment, variation in the amount of radium irradiation administered, and more especially in the time required to administer it, is of more importance than variations in the x-ray therapy, provided excessive x-ray dosage is avoided. In the earlier series, many of the patients who developed severe urinary tract damage had received no x-ray therapy, and several of them had received less than 3,000 mc. hr. of radon. However, in all of them the radon had been administered rapidly without anesthesia, and therefore without the possibility of as careful packing of the vagina as can be accomplished in the anesthetized patient.

In our second series of patients who received 4,800 mg. hr. of radium and 8,000 to 10,000 r. of x-ray there was no urinary tract damage in the patients who survived five years or more, but the radium was administered by two 24-hour applications of 100 mg. of radium with an interval of two weeks between treatments. In our third small series of patients who received the same x-ray dosage, but in whom the radium dosage was increased to 6,000 mg. hr. by increasing the amount of radium by 25 per cent, but leaving the time

but the patient continued to bleed profusely. An attempt was made to ligate the hypogastric arteries but because of the adhesions and induration in the pelvis, they could not be isolated. An intravenous pyelogram at this time revealed a functionless right kidney, and on cystoscopic examination a No. 6 ureteral catheter would pass for only 2 cm. up the right ureter. The patient died suddenly the next day after an exsanguinating hemorrhage. Autopsy revealed massive induration and fixation of all the pelvic structures. There was a large rectovaginal fistula, and in the right parametrial region was an irregular cavity measuring 4 cm. in diameter. A segment of the right ureter the length of the cavity was completely destroyed, so that the remaining upper and lower portions of the ureter communicated with the cavity (Fig. 12). Numerous microscopic sections from the pelvic organs failed to reveal any persistent carcinoma cells. This case is undoubtedly one of rectovaginal fistula, destruction of the ureter with functionless kidney, and death resulting from irradiation therapy.



Fig. 12.—Autopsy specimen from a patient dying of hemorrhage from the bowel nine months following irradiation treatment (6,000 mg. hr. of radium and 10,000 r. of deep x-ray therapy at 400 KVP.) for Stage II carcinoma of the cervix. Note the necrotic cavitation in the right broad ligament region and complete destruction of a segment of ureter in the same region. There was also a large rectovaginal fistula. No remaining carcinoma was found in the sections.

CASE 2.—Our second recent case of severe damage to the urinary tract is that of a 38-year-old Negro para iii with an old history of right pulmonary tuberculosis for which she had had the right lung collapsed by pneumothorax for six years. There was also a history of essential hypertension. She was seen in January, 1947, complaining of menorrhagia, and was examined many times between January and October of the same year. During this period a total of four biopsies was taken, the first and last of these showing intraepithelial carcinoma. In October, pelvic examination revealed a cervix which was covered with normal-looking mucosa. The fundus was on the upper border of normal in size and both adnexa were normal. Although it is customary in our clinic to treat non-invasive carcinoma of the cervix by means of the modified Wertheim operation, it was

## Discussion

DR. JOHN B. MONTGOMERY, Philadelphia, Pa. (by invitation).—Dr. Everett's three groups of carefully studied patients show clearly the accidental effect of various plans of irradiation therapy of carcinoma of the cervix upon the urinary tract and surrounding tissues and also demonstrate the value of repeated urologic studies in the management of this lesion. In his first group of patients comparatively small amounts of irradiation with radium administered quickly resulted in a rather high incidence of urinary tract and local tissue damage. On the other hand, larger amounts of irradiation administered less rapidly in conjunction with x-ray therapy have provided adequate treatment in the second group with practically no urinary tract damage that could be attributed to the irradiation. In Dr. Everett's third group of patients, it is interesting to note that, in the presence of roentgen therapy, administered as 2,500 r. to each of four portals, increasing the radium dosage from 4,800 mg. hr. to 6,000 mg. hr., or apparently by only 25 per cent, resulted in a tremendous increase in severe local tissue reactions. This increase was accomplished by adding 25 mg. of radium to the lower half of the 50 mg. tandem application to the cervical canal, thereby actually doubling the dose in the area that was already receiving the most intense irradiation by virtue of the cross fire from the 50 mg. plaque placed against the cervix. This is shown graphically in the isodose curves that Dr. Everett has prepared but has not had time to present. The resulting high intensity irradiation applied to a small area probably was the main factor in producing the severe local reaction. Dr. Everett's present plan of administering deep roentgen therapy (2,500 r. to each of four portals) followed or preceded by the application of 4,800 mg. hr. of radium in two doses of 2,400 mg. hr. each at two-week intervals has proved to be far superior. This plan is similar to that in use on the Division of Gynecology in The Jefferson Medical College Hospital, except that we apply 3,600 mg. hr. of radium at one sitting beginning three to four weeks after completion of roentgen therapy.

Since 1942, we have endeavored to increase this amount of irradiation to the cervix without damaging the bladder by supplementing the external irradiation (2,000 r. to four portals) prior to the local radium application (3,600 to 4,000 mg. hr., intracavitary and interstitial) by transvaginal roentgen therapy (2,000 to 2,500 r.). The incidence of local tissue injury, following this plan, has not yet been evaluated but it is our impression that, although there may be some increase in bowel irritation of moderate degree, there has been no increase in injuries to the urinary tract.

This experience of Dr. Everett in applying increasing amounts of irradiation to the cervix in the hope of accomplishing more complete destruction of the tumor no doubt has been shared by many of us. It is often difficult for the gynecologist, who bears heavy responsibility in treating these unfortunate women, to realize that there is an optimum irradiation dose beyond which even comparatively small increases may be harmful. On the other hand, some individuals are unusually susceptible to irradiation therapy and may suffer severe tissue damage from a dose that is well tolerated by others. This was clearly illustrated by two of our patients who were treated in June and July, 1939. Both were moderately obese white women. One was 51, the other 44 years of age. Each had a squamous-cell carcinoma of the cervix of approximately the same extent, Stage II or early Stage III, Schmitz. Six weeks after the administration of deep x-ray therapy in the form of 2,000 r. to each of four portals radium was applied according to our usual plan. One 50 mg. capsule screened with 1.5 mm. of platinum was inserted into the cervical canal and ten 10 mg. needles screened with 0.5 mm. of platinum were inserted around the periphery. The usual application of 3,600 mg. hr. was increased to 4,500 mg. hr. One patient developed slight local necrosis and mild bladder symptoms but recovered and is now well and apparently free of disease. The other patient developed extensive local necrosis and died of sepsis seven months after treatment. Autopsy revealed extensive necrosis of all pelvic tissues but no evidence of carcinoma.

The value of repeated urologic study is shown most clearly by Dr. Everett in the group of patients who were treated with high-intensity radium therapy prior to 1939.

required for administration the same, there has been a high percentage (31 per cent) of severe postirradiation reactions.

At the University of Maryland Hospital from which Diehl and Hundley have reported no demonstrable evidence of urinary tract damage, and where the technique of radium application was very similar to ours, 6,000 mg. hr. of radium are routinely given. However, only 100 mg. were used for two applications of 30 hours each with an interval of three weeks between the two. This was followed by 6,000 to 8,000 r. of x-ray which was repeated after twelve weeks. In a recent article, Kimbrough and Muckle have reported the results of their technique at the Pennsylvania Hospital which also consists of the administration of 6,000 mg. hr. of radium, using only 60 mg. of the element which is left in place for 100 hours either as a single application or as two applications a month apart. Their x-ray dosage is small, 2,000 to 2,800 r. They have encountered a negligible amount of postirradiation reaction.

Morton and Kerner have recently described the technique used at the University of California. Two radium applications are administered two weeks apart. The first of these consists of 150 mg. (three 50 mg. capsules) within the cervix for a total of 3,000 mg. hr. At the second treatment 100 to 150 mg. of radium are applied against the cervix for a total of 1,500 mg. hr. Their standard x-ray dosage is 12,000 r., 3,000 r. to four pelvic fields using either a 200 or a 1,000 kv. machine. These authors have reported on all types of reactions which apparently have been considerably more frequent than have been noted by others using smaller quantities of radium over longer periods of time.

### Conclusions

From the study here reported we believe that the following conclusions are justified:

1. The urological study of patients before and at repeated intervals subsequent to treatment of carcinoma of the cervix by irradiation therapy is a valuable procedure.
2. Such studies aid in the estimation of prognosis, the determination of response to treatment, the early detection of late recurrence of the cancer, and the detection of urinary tract damage resulting from the treatment.
3. The early detection of such irradiation damage to the urinary tract makes possible appropriate treatment before ureteral obstruction has advanced to such a degree as to endanger the life of the patient.
4. Radium is potentially more dangerous than x-ray therapy in so far as the production of urinary tract damage is concerned.
5. The potential danger to the urinary tract and other normal structures from radium irradiation is reduced by achieving the desired milligram hour dosage with smaller amounts of radium administered over longer periods of time.

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Fig. 10 shows the distribution of irradiation to the pelvis when the larger irradiation dose, 6,000 mg. hr., was used in conjunction with 400 kv. x-ray therapy. The dosage to the cervix is quite high and it is not surprising that we ran into a high incidence of irradiation reactions with this technique. As Dr. Everett has stated, the incidence of reactions of all types is 31 per cent and there was severe ureteral damage in at least 5 per cent. Since these patients were all treated since the war, we do not know yet what the five-year salvage will be but we think it will be respectable in spite of the high incidence of irradiation reactions. Needless to say, we have discontinued this last technique and are now using 4,800 mg. hr. total radium dosage, in conjunction with 400 kv. x-ray delivered over four external portals, and in addition we are using a vaginal cone angled toward the fornices, in an attempt to deliver additional irradiation to the parametrium. Dr. Everett and I plan to continue this study and should have another report ready in another 10 years.

DR. J. MASON HUNDLEY, JR., Baltimore, Md.—Wishing to learn if radiation of the malignant cervix produced changes in the ureteral wall, we began a study\* of this problem in 1937. A group of 37 patients with carcinoma of the cervix was selected for complete urological studies. Of these, 11 were in Grade I and 2 of these showed dilatation of the tract before therapy; 9 were in Grade II and 1 showed dilatation of the tract before therapy; 17 were in Grade III and 7 of these showed dilatation of the tract before therapy.

The patients were then given radium application in broken doses, 3,000 mg. hr. in two treatments three weeks apart, making a total of 6,000 mg. hr. This was followed in three weeks by a cycle of deep x-ray therapy of 7,000 r. Twelve weeks later another cycle of 7,000 r. was given.

One year later another urographic study was carried out and the following results were noted: No patients in Grades I and II showed development of dilatation. In Grade III, 7 patients originally showed dilatation; 6 of these showed no appreciable change between the two urographic studies, and the remaining patient showed increasing dilatation and eventual death from carcinoma. Of the remaining 10 patients, 4 developed dilatation, 3 of them dying with carcinoma and associated marked urinary tract dilatation in less than two and one-half years. The one remaining patient with minimal dilatation lived seven years and three months and died of carcinoma.

Believing that urinary tract changes, i.e., hydroureter and hydronephrosis, might possibly develop at still a later date, another urographic study was carried on by the intravenous method more than nine years later. Results of this third intravenous urographic study made on the twenty survivors follows: One urogram made twelve years after the original study showed slight increase in degree of dilatation; the remaining patients studied showed either normal urograms or no increase in the pre-existing pathology.

Of the original 37 patients investigated at the onset, the survival rate is now as follows:

One patient was lost track of, having moved to New England after 1946, but at that time she was doing well, six years after her first visit.

Over-all survival, 5 years, 70.2 per cent.

Over-all survival, 8 years, 54.0 per cent.

Important factors to be considered for good results are: (1) small amount of radium with heavy filtration; (2) prolonged radiation; (3) proper application of pack, and (4) maximal vaginal packing. The proper packing of the vagina is of importance for it occasions considerable displacement of the focal point so that the ureter receives a minimum of radiation.

In conclusion, we believe, from our studies, that radiation of the malignant cervix plays a minimal role, if any, in the production of dilatation changes in the urinary tract.

\*Note: This article with the exception of the third urographic study appears in Surg., Gynec. and Obst. for December, 1948.

These studies revealed not only a relatively high incidence of urinary tract obstruction in patients so treated but they have shown that these injuries have persisted and in some instances have progressed in the small group of patients who have survived and who apparently are free of malignancy. The importance of the early recognition and careful repeated follow-up study of such lesions cannot be overemphasized. As Dr. Everett suggests, they are probably due to progressive irradiation fibrosis, yet in occasional instances obstruction of the ureter has been the first sign of recurrence of the carcinoma.

In those patients treated from 1940 to 1942 with roentgentherapy and a less intense application of radium, repeated urologic examination revealed no instance of urinary tract damage attributable to irradiation. This is an enviable record and it is undoubtedly influenced by the care and skill with which the treatment was carried out as well as to the reduction in the intensity of the irradiation. It is of interest to note in this group that coincidental urethral obstruction present before treatment in seven of fifteen patients with Stage I carcinoma was not influenced unfavorably by the irradiation therapy.

Our experience with irradiation therapy in carcinoma of the cervix in general has been similar to that of Dr. Everett. The recent figures presented by Dr. Scheffey before the Medical Society of the State of Pennsylvania in September, 1948, show a relative five-year survival of 38 per cent in patients treated from 1936 to 1943. In 116 patients with all stages of carcinoma studied by intravenous urography, following therapy, between Sept. 1, 1943, and Sept. 1, 1945, we found urinary tract obstruction in 62, or 53.4 per cent. Approximately 25 per cent of the patients who had originally Stage I and Stage II lesions showed some evidence of ureteral obstruction. All were of mild degree except one which was proved later to be due to an extension of the disease. More than 50 per cent of Stage III patients and a somewhat greater percentage of those with more advanced lesions were found to have obstructions that were considered to be of clinical significance. In the small group of our patients who have had urologic studies both before and after treatment, we have noted, as has Dr. Everett, that ureteral obstruction before treatment in Stage III patients was a grave prognostic sign, all such patients having died within one year.

The importance of persistent upper urinary tract damage in patients who have responded satisfactorily to irradiation therapy is illustrated by one patient who was treated for Stage III carcinoma by our usual planned technique in March, 1941. Her convalescence was uneventful but she continued to have moderate induration in the right parametrium. In March, 1942, one year after completion of her treatment, she was readmitted in critical condition with abdominal pain, distention, and vomiting. The admitting diagnosis was extensive recurrent carcinoma of the cervix with peritonitis. Further study revealed extensive urinary tract infection with complete obstruction of the right ureter and right hydronephrosis. After removal of the kidney, the patient recovered completely and is now living and apparently free of malignancy.

Incidents such as this, which have occurred not infrequently in our experience, together with the results of Dr. Everett's carefully repeated studies, have convinced us that urinary tract studies before treatment and at intervals thereafter may be of considerable importance in the management of the patient with cervical cancer.

DR. C. BERNARD BRACK, Baltimore, Md. (by invitation).—As Dr. Everett has stated, we are convinced that intensity is the most important single factor in producing urinary tract damage. However, in our last series of cases where there was an increase in the incidence of urinary tract complications, we increased the quantity of radium dosage to the cervix and to the paracervical tissues as well as increasing the intensity of the irradiation. This is illustrated by Fig. 11 in Dr. Everett's paper, which shows the intensity of the irradiation with our original technique. The dosage was very high—34,500 r. delivered to the tissues at the center of the cervix. However, with this technique, we had little urinary tract damage. The incidence of vesicovaginal fistula was 6 per cent. The incidence of all complications was 11 per cent and did not exceed 17 per cent in any one year. The corrected five-year salvage over a three-year period was 26 per cent and in one year was almost 33 per cent.

# THE LYMPHATIC SPREAD OF CARCINOMA OF THE CERVIX AND OF THE BODY OF THE UTERUS\*

## A Study of 420 Necropsies

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THE revival of interest in the surgical treatment of carcinoma of the cervix<sup>6, 8, 33, 34, 36, 46, 48</sup> emphasizes the need for further study of this disease on an anatomical and pathological basis. Unfortunately, there is no exact means of determining the true extent of the clinical spread of the cancerous growth, except by necropsy. The study of necropsy material has its limitations, but it does permit a thorough examination of the ravages of the malignant disease and a correlation of the pertinent findings between the treated and the nontreated cases.

### The Material

The 420 cases in this series include 64 cases of adenocarcinoma of the corpus uteri, and 356 cases of carcinoma of the cervix. The cervical series also includes adenocarcinomas of the cervix (fourteen cases) and in addition, carcinoma of the cervical stump (thirty-two cases). The series is further divided into the treated and the nontreated groups. "Treatment" consisted of radiation therapy, and, in most instances, included x-ray and radium.

The classification of the League of Nations<sup>27</sup> has been followed in classifying the clinically determinable extent of the cervical carcinoma. The nontreated cases are classified according to the clinical interpretation of the extent of the disease at the time of the patient's last admission to the hospital.

The clinical classification of the treated case was established at the time of the first treatment. It is well known that the clinical estimation of the extent of the disease is imperfect and this is substantiated in our study by an error of over 25 per cent when the clinical estimate is compared with the findings at necropsy. In most instances, inflammatory induration of the parametrium was misinterpreted as clinical evidence of malignant extension.

Careful lymph node dissections were done on twenty-six nontreated and fifteen treated cases of carcinoma of the cervix and ten cases of corporeal adenocarcinoma. In each case the nodes were properly segregated, and in addition one block was taken through each parametrium. An average of four sections was made of each block, serial sections being impractical.<sup>26, 41, 42</sup> Obviously this less complete method of examination will overlook some metastases. Therefore the figures presented in this study may not represent the actual incidence of metastases.

### The Lymphatics of the Cervix (Fig. 1)

The pathways of the lymphatic vessels and the anatomical sites of the nodes have been carefully studied by many observers.<sup>11, 22, 39, 40, 43, 45</sup> From our observations it is permissible, we believe, to separate the lymphatic nodes into primary and secondary groups.

\*Presented at the Seventy-Second Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 16 to 18, 1949.

DR. EVERETT (Closing).—Our objectives in these studies are to determine the best method of irradiation to acquire the highest salvage rate and at the same time avoid destruction of normal tissues. I would have been very much interested if Dr. McKelvey had mentioned complications in his studies. From our study I would think his complications would be very low because he uses very small doses of radium over a long period of time, and our studies would seem to indicate that that is the answer.

Dr. Hundley is fortunate in not having had many urologic complications, but he has given the radium slowly. I believe that we have proved that if you step up the speed with which you give irradiation you get complications. We have worked on this for nearly twenty years. Our results have improved and in another ten years I hope to be able to bring in a report with a salvage rate equaling Dr. McKelvey's and with no urologic complications.



I. *The Primary Group.*—

A. *The Parametrium:* The presence of small lymph nodes along the major lymphatic trunks traversing the parametrium is constant enough to permit their inclusion as a separate chain of lymph nodes.

B. *The Paracervical (Ureteral) Node:* Located near the crossing of the uterine artery and the ureter, this node was not recognizable in 8 per cent of the treated cases and in 3 per cent of our nontreated cases of cervical carcinoma.

C. *The Hypogastric Nodes:* The uniformly small nodes in this group vary in number and location, and are located along the course of the hypogastric vein, near its junction with the external iliac vein.

D. *The Obturator Nodes:* These are frequently described as one large node (Leveuf's node<sup>28</sup>). We have found as many as three distinct nodes, associated with the obturator vessels and nerve, near the obturator foramen.

E. *The External Iliac Nodes:* This group varies in number from three to eight nodes, which tend to be uniformly larger than the nodes of the other groups. Usually located in the sulcus between the external iliac artery and vein, they may be found entirely on the mesial surface of the vein.

II. *The Secondary Group.*—

A. *The Sacral Nodes:* This group includes the several nodes in the sacral concavity and on the sacral promontory.

B. *The Common Iliac Nodes:* These vary in number and location, but usually lie on the mesial and lateral surfaces of the common iliac vessels, just below the bifurcation of the aorta.

C. *The Inguinal Nodes:* These include the deep and superficial femoral lymph nodes.

D. *The Aortic (Periaortic) Nodes:* These extend from the level of the bifurcation of the aorta to the diaphragm, and they lie on the superior and the lateral aspects of the aorta.

The lymph channels and node sites are often variable due to the ever-present intercommunicating subsidiary vessels and the relatively inconstant locations, exhibited by some of the major nodes. It was also not uncommon to find anomalous nodes along the lymph vessels connecting the major node groups. These intercommunicating vessels account for the unpredictable sites of some of the metastases.

The lymphatic vessels draining the cervix converge at the level of the junction of the cervix and the corpus to form the paracervical plexus, from which main trunks pass laterally, and follow the direction of the uterine veins. Between these main trunks are intercommunicating vessels, which permit the occasional by-passing of a major node group located along the main lymphatic route.\*

*Channel 1:* Arising from the paracervical plexus and following the direction of the uterine artery, this channel connects with the paracervical, the external iliac, and the obturator nodes.

*Channel 2:* This channel also arises from the paracervical plexus, follows the course of the uterine vein posteriorly, to terminate in the hypogastric nodes. Intercommunicating vessels permit frequent metastases between the hypogastric, the obturator, the external iliac, and the sacral node groups.

*Channel 3:* This is a smaller and less constant channel which passes forward and then backward along the uterosacral folds on both sides of the rectum, to terminate in the sacral nodes located in the concavity and on the promontory of the sacrum. Though this node group is included as a part of the secondary group of nodes, intercommunicating channels frequently permit metastases to the hypogastric nodes, before the sacral nodes are involved. These subsidiary channels are so constant that it is permissible to interpret them as major routes.

\*Injection of "Pantomine Sky-blue" (E. I. du Pont de Nemours & Co., Inc.) into the cervix prior to laparotomy frequently permits an easy tracing of the lymph channels and the localizing of the nodes.

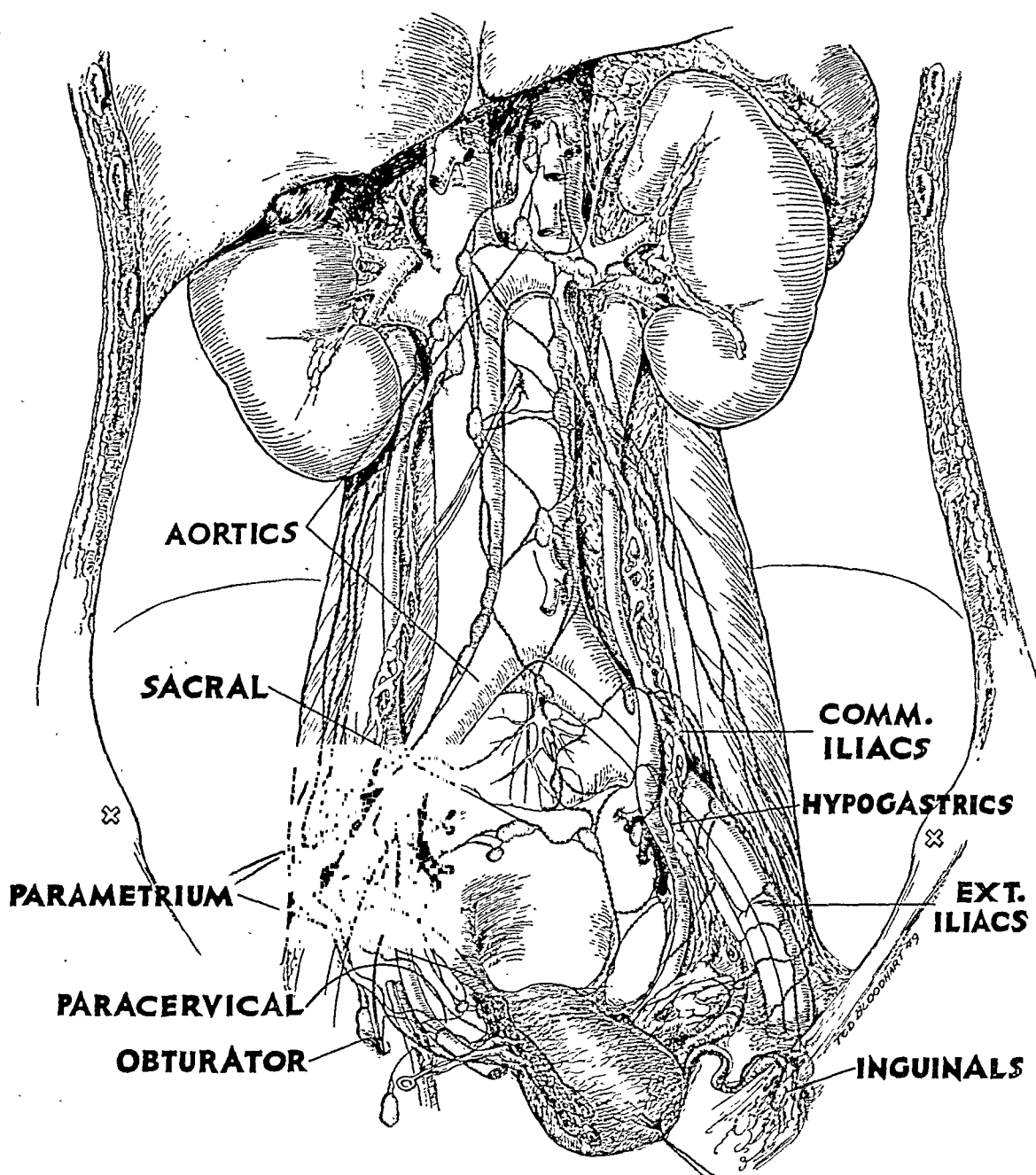


Fig. 1.—Lymph vessels and lymph nodes of the cervix and the body of the uterus.

static deposits in the parametrium. There was a total of thirteen primary and seven secondary group node metastases and one distant metastasis. That lymphatic extension does not occur at a constant rate is supported by the fact that unilateral node involvement is not uncommon where the parametria are equally involved.

*Clinical Stage IV*, seven cases: Bilateral involvement of the parametrium in six of the cases. Twenty primary group nodes, nine secondary group nodes, and six distant metastases were present in this group.

TABLE I. INCIDENCE OF NODE GROUP INVOLVEMENT IN TWENTY-SIX NONTREATED CASES OF CERVICAL CARCINOMA

	Parametrium		Paracervicals		Obturator		Hypogastric		Ext. Iliacs		Com. Iliacs		Inguinal		Sacral		Aortics		Dist. Metas.	
	RT	LT	RT	LT	RT	LT	RT	LT	RT	LT	RT	LT	RT	LT						
STAGE I (5)	-	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
STAGE II (6)	3	2	2	1	-	2	1	-	1	-	-	-	-	-	1		1		-	
STAGE III (8)	8	7	3	3	4	3	1	2	3	1	3	-	1	1	1		2		1	
STAGE IV (7)	7	6	3	2	5	3	4	5	3	2	5	1	-	-	4		4		6	

TABLE II. INCIDENCE OF NODE GROUP INVOLVEMENT IN FIFTEEN TREATED CASES OF CERVICAL CARCINOMA

	Parametrium		Paracervicals		Obturator		Hypogastric		Ext. Iliacs		Com. Iliacs		Inguinal		Sacral		Aortics		Dist. Metas.	
	RT	LT	RT	LT	RT	LT	RT	LT	RT	LT	RT	LT	RT	LT						
STAGE I (3)	-	-	-	-	-	-	1	1	-	-	-	-	-	-	-		1		-	
STAGE II (10)	3	3	6	5	2	3	6	8	8	6	5	3	1	1	3		3		7	
STAGE III (1)	-	-	-	-	1	1	-	1	1	1	1	-	-	-	1		-		-	
STAGE IV (1)	1	1	-	1	1	1	-	-	1	-	1	-	-	-	-		1		1	

B. Carcinoma, Cervix Uteri, fifteen treated cases (Table II).—

*Clinical Stage I*, three cases: The parametrium was fibrous but there was no evidence of metastasis. The channels were suggestively smaller than in the nontreated group and several of the nodes were completely hyalinized. One case had metastases to the hypogastric groups with one small cancerous node in the aortic group (two years postirradiation). All of these cases died of uremia secondary to ureteral obstruction (twenty-four, nine, and nineteen months, respectively, postirradiation).

*Clinical Stage II*, ten cases: Normal parametrium in two cases (twenty-nine and thirty-three months). Marked fibrosis of the parametrium occurred in five cases (thirteen, seven, nineteen, thirty-seven, and thirty-three months postirradiation). Nine of the cases had twenty-eight primary group nodes and nine secondary group nodes, and seven cases had distant metastases. Seventeen of the primary group nodes showed marked hyaline changes.

### The Lymph Nodes<sup>36, 46, 47, 51</sup>

It is difficult to interpret correctly the pathological status of a node either at operation or necropsy. Enlargement of a node is not pathognomonic of metastasis. Alteration in size may be due to an inflammatory process while a small adjacent node may contain carcinoma. As a rule, however, large adherent or necrotic nodes are malignant. In this study, the error of our ability to estimate properly the presence or absence of cancer from the gross appearance of the node at necropsy was approximately 20 per cent.

Normal lymph nodes vary not only in size and histological structure in different individuals, but such variations may be readily noted in the same individual. It is not uncommon to find enlarged, but histologically normal nodes in close proximity to nodes containing cancerous cells. In this series no constant histological changes in the nodes attributable to the effect of irradiation were found. The marked fibrosis and hyalinization usually interpreted as an indication of the effects of prolonged and intensive irradiation were also present in some of the nodes from the nontreated cases. Evidence of node disintegration is more common in the treated cases. The nodes of 17 per cent of this group, located within the accepted range of the effect of irradiation, exhibited no disturbance of their histological patterns. On the other hand, over 12 per cent of the nontreated cases had nodes which showed the changes generally attributed to the effects of irradiation. It has been impossible, from our observations, to determine the amount of irradiation by the changes within the node. Minute islands of malignant cells are occasionally found within a thickened, fibrous and hyalinized node, but we are not prepared to correlate, however, the effect of irradiation upon the metastasis. Some of these malignant inclusions appear so completely encapsulated as to prevent further growth, but it is also probable that their growth is only temporarily restrained. In 4 per cent of the treated and 7 per cent of the nontreated cases, we found small glandular inclusions interpreted by some as probable islands of endometrial glands.

### Part I

The careful dissection of the lymph nodes and parametria in forty-one cases at necropsy offered a fairly consistent pattern of carcinomatous dissemination in carcinoma of the cervix. The size of the series does not permit the indexing of the nodes according to their order of involvement, but it is apparent that one or both parametria, and one or more nodes of the primary group, are usually involved before metastases extend to nodes of the secondary group. This material is set forth briefly.

*A. Carcinoma, Cervix Uteri*, twenty-six nontreated cases (Table I).—

*Clinical Stage I*, five cases: These patients died of conditions unrelated to the cervical growth. Though there was no parametrial induration, unilateral involvement of the paracervical node was present in two cases. Three of the patients had non-neoplastic induration of the parametria with nonmalignant enlargement of the primary group of nodes.

*Clinical Stage II*, six cases: Unilateral involvement of the parametrium occurred in five of the six cases, while associated inflammatory-type induration of the parametrium occurred in four of the cases. Two of the cases had a total of seven metastatic nodes, including nodes of the secondary group. Eleven nodes showed an inflammatory enlargement. Three of this group died of causes unrelated to the malignant growth; two died from operative shock following attempted radical surgery; one died of uremia secondary to unilateral malignant induration of the parametrium.

*Clinical Stage III*, eight cases: Bilateral involvement of the parametrium occurred in seven of the eight cases. Five of these cases exhibited small meta-

tases in the parametrium, and the increased frequency of distant metastases in the treated group. Therefore, on this small series, it is permissible to deduce that the irradiation probably destroyed some of the local metastases.

Distant metastases were present in 53 per cent of the treated and 27 per cent of the nontreated cases, suggesting the probable arresting effect of extensive irradiation on the local growth and involved nodes. That too much credence cannot be given this marked variation in incidence is supported by the presence of distant metastases in 37.8 per cent of the treated and 32.5 per cent of the nontreated cases in the entire series of 356 cases. This emphasizes the inherent danger of statistics based on a few cases. There was no involvement of the nodes of the secondary group without metastases present in the major primary nodes, though node involvement was present in two cases where there was no evidence of malignant extension to the parametrium.

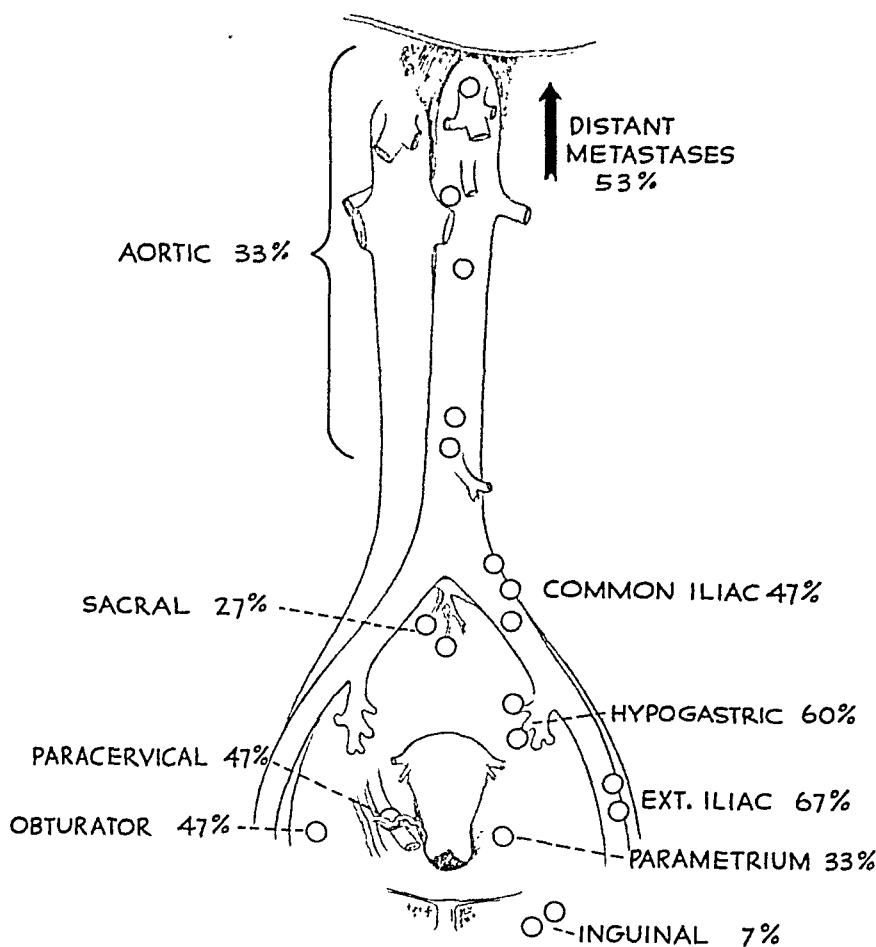


Fig. 3.—Incidence of node group involvement in fifteen treated cases of cervical carcinoma.

## Part II

The 356 cases of cervical carcinoma, including the forty-one cases just described, are divided into a treated and nontreated group. Of the treated cases 42.6 per cent were treated under the auspices of the California Institute of Technology, the remainder either at the Los Angeles General Hospital or in private clinics. The material is set forth in Table III.

### *Node Involvement.*—

The nontreated cervical series had a total of 44.7 per cent involvement of the primary group nodes, 39 per cent of the secondary group nodes, and 32.5

*Clinical Stage III*, one case: Two years following intensive irradiation, the parametrium was fibrous but free of metastasis. Nodes of both groups were involved and the patient died of uremia.

*Clinical Stage IV*, one case: Eighteen months after intensive irradiation, small isolated nodes with metastatic inclusions were present in the parametria; there were metastases to both node groups and the patient died from the metastases to the lung.

*Node Involvement.*<sup>3, 4, 7, 26, 31, 33, 34, 38, 43, 44, 54</sup>—

Correlating the involvement of the lymph nodes in this relatively small series of treated and nontreated cases of carcinoma of the cervix, studied at necropsy, by careful dissection and multiple sections, several facts are apparent. This material is presented in Figs. 2 and 3.

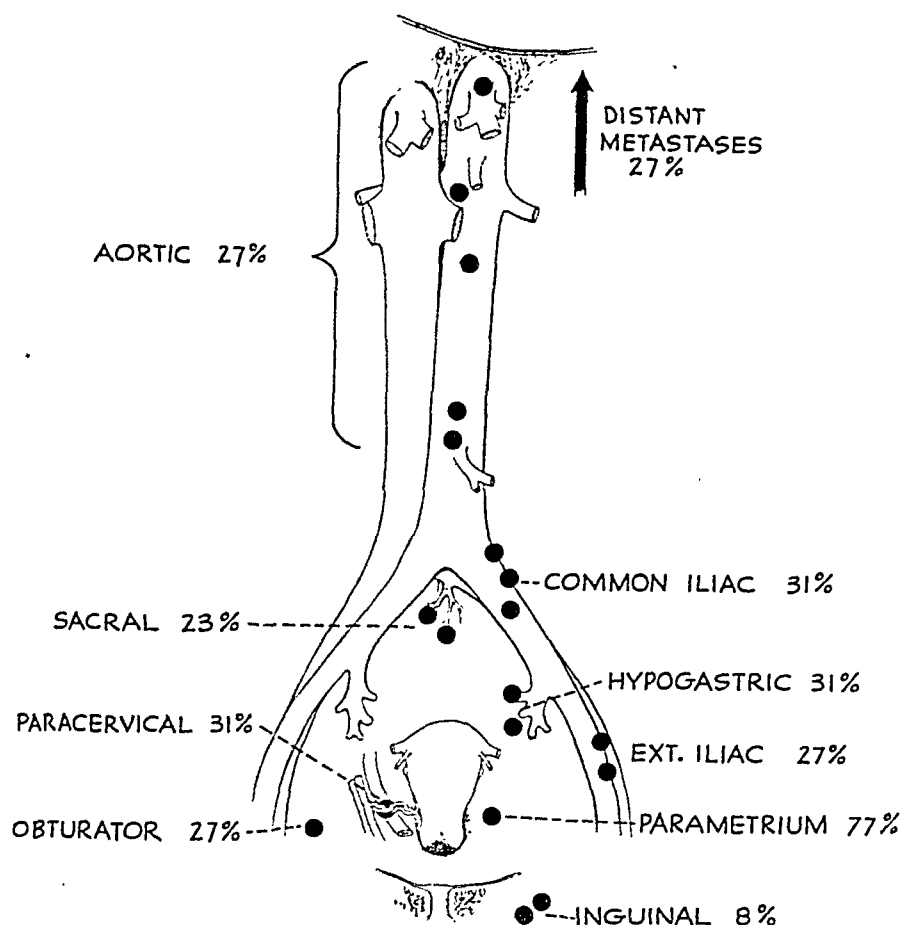


Fig. 2.—Incidence of node group involvement in twenty-six nontreated cases of cervical carcinoma.

Whereas the parametrium of the patients in the nontreated group revealed cancerous infiltration in 77 per cent of the cases, it occurred in only 33 per cent of the treated cases. The marked irradiation effect was manifested by extensive fibrosis of the parametrium, though in only approximately 70 per cent of the cases did the nodes show any of the changes usually attributable to deep irradiation. Nor were all of the small parametrial nodes containing metastases sterilized by the therapy. Whether the unaffected nodes were sterilized by the radiotherapy or were free of metastases before treatment cannot be stated. That the irradiation has some effect, is demonstrated by the lessened frequency of metas-

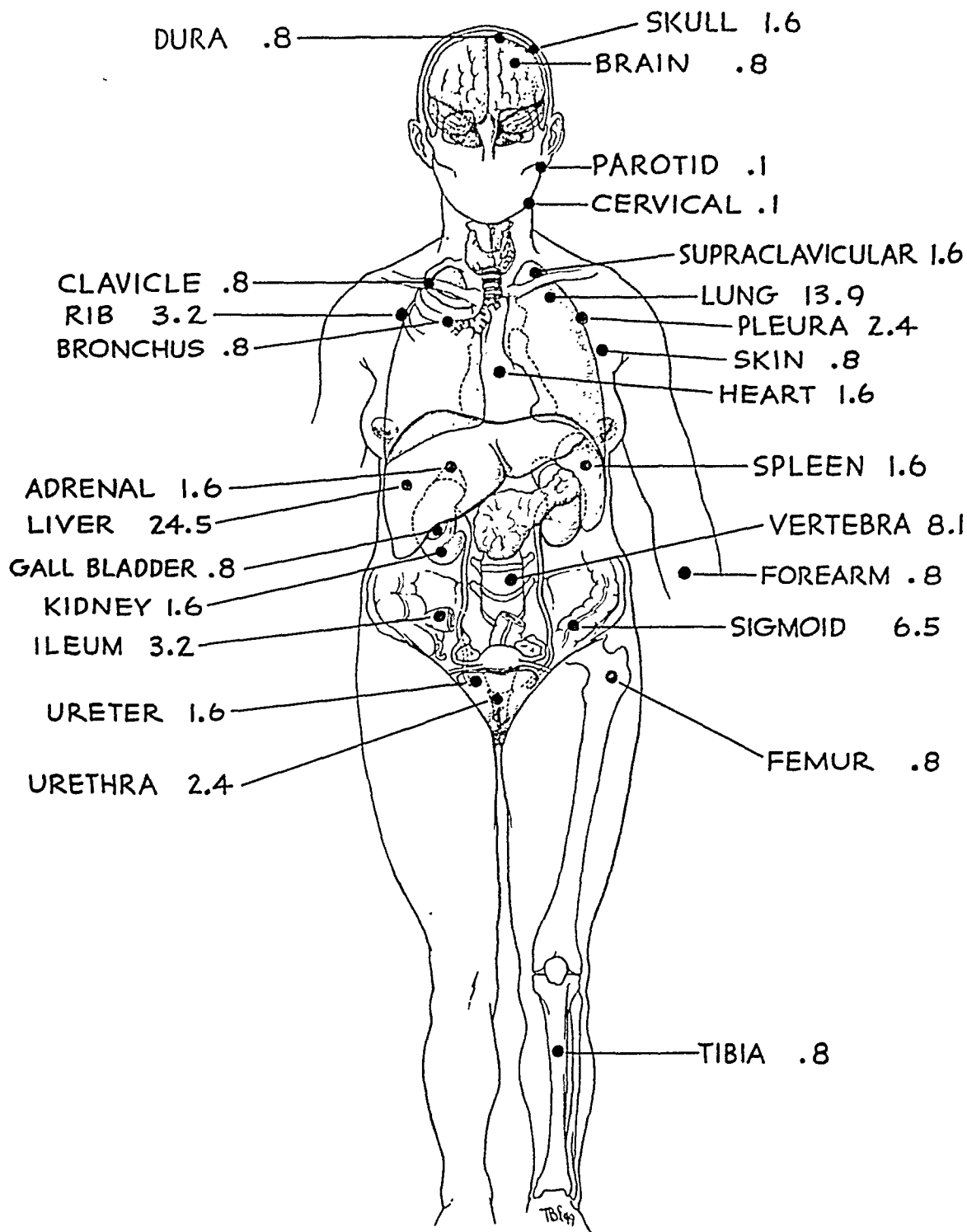


Fig. 4.—Incidence of distant metastases in 154 nontreated cases of cervical carcinoma.

per cent with distant metastases. The treated series had an involvement of 58.5 per cent of the primary group nodes, 70 per cent of the secondary group nodes, and distant metastases in 37.8 per cent of the cases. Though the incidence of node group involvement varies considerably, the frequency of distant metastases is practically identical. Several factors must be considered in interpreting these differences; first, the variation in the time element as regards the clinical classification of the disease; second, the accepted 20 to 30 per cent error in the clinical interpretation of the stage of extension; third, the probable importance of radiotherapy as an impedimentary factor on the metastatic nodes.

TABLE III. INCIDENCE OF NODE GROUP INVOLVEMENT IN 356 NONTREATED AND TREATED CASES OF CERVICAL CARCINOMA

		PRIMARY NODES (PERCENT)	SECONDARY NODES (PERCENT)	DISTANT METASTASES (PERCENT)
<i>Stage I</i>	TREATED	85	85	41
	NON TREATED	2	—	—
<i>Stage II</i>	TREATED	77	65	37
	NON TREATED	20	4	2
<i>Stage III</i>	TREATED	50	58	26
	NON TREATED	31	27	15
<i>Stage IV</i>	TREATED	52	53	57
	NON TREATED	67	64	62
<i>Total</i>	TREATED	58.5	70	37.8
	NON TREATED	44.7	39	32.5

The involvement of 20 per cent of the primary group nodes in the non-treated *Clinical Stage II* cases is higher than expected. Of the 42.6 per cent treated at the California Institute of Technology, 50 per cent showed a local cure within a minimum of three months, a maximum of seven and one-half years, and an average of 2.8 years, following irradiation.

*Distant Metastases.* 1, 2, 5, 10, 19, 20, 37, 46, 52, 53, 54—

The frequency of distant metastases in cases of carcinoma of the cervix is not widely appreciated. This is especially true of those cases with pulmonary or bone metastases. Examining the material in Figs. 4 and 5 it is noted that distant metastases occurred in 32.5 per cent of the nontreated, and 37.8 per cent of the treated cases. The liver was the most frequent site of metastases, with the bone, lung, and bowel involved in that order. The slight variation in organ involvement in the two groups permits no significant explanation as to the effects of irradiation.

The unusual sites include the brain with occasional blindness. Several of the cases with bone metastases were treated as primary destructive bone lesions. There was primary involvement of the ureter in 2.1 per cent of the cases.<sup>9, 13</sup> The possible wide dissemination of the disease is further emphasized by the presence of metastases in the skin of the chest, the axillary nodes, the cervical nodes, the pituitary gland, and the parotid gland. The involvement of the left supra-clavicular node (Virchow's node<sup>49</sup>) in the presence of cervical carcinoma is of interest since this node is usually mentioned as a common site of metastases from cancer of the stomach.



## The Assigned Cause of Death

In 1843, Dewees wrote that "patients rarely die during the carcinomatous stage of the disease; when they do, it is a consequence of frequent hemorrhage." Fifty years later, Dudley stated that, "in the vast majority of cases death is from marasmus or uremia, or both." Cullen in 1900 wrote that, "death is due to some intercurrent affection, usually to pneumonia or extensive renal disease." More recently, Warren and Ewing stated that complications arising from ureteral obstruction is the most common cause of death. This agrees with most observations.<sup>5, 7, 10, 12, 18, 20, 26, 37, 50</sup>

In this series, uremia was the assigned cause of death in 58.5 per cent of the nontreated cases and 49.3 per cent of the treated cases. However, an added 24.3 per cent of the nontreated cases had evidence of ureteral compression with hydronephrosis. In the treated series, the secondary ureteral involvement was 29.3 per cent, thus 82.8 per cent of the nontreated and 78.6 per cent of the treated cases had evidence of ureteral compression and kidney damage.<sup>16, 17, 21, 25, 37, 42</sup> Cachexia, hemorrhage, intestinal obstruction, and peritonitis accounted for the remainder of the patients dying as a result of this disease. There were 8.6 per cent of the nontreated and 6.4 per cent of the treated cases who died of causes unrelated to the malignant growth.

## Part III

### *Adenocarcinoma, Corpus Uteri*, sixty-four cases.—

The series of sixty-four cases of corporeal carcinoma does not permit the separation into treated and nontreated groups as none of the cases received irradiation therapy. The clinical stage of the extent of the cancerous growth follows the classification of Healey and Cutler,<sup>24</sup> and was established at the last admission of the patient to the hospital. In 14.2 per cent of the cases, the diagnosis was not made prior to autopsy.

### *The Lymphatic of the Uterus* (Fig. 1).—

The rich plexus of lymphatics draining the corpus uteri converge to form three main channels.

*Channel I:* The lymphatic vessels from the lower and midportions of the uterus are closely associated with the major trunks from the cervix and metastasize in a similar pattern.

*Channel II:* The lymphatic vessels of the upper portion of the uterus join with the vessels from the adnexa and follow the direction of the ovarian vessels, draining directly into the nodes of the aortic group. Subsidiary vessels permit involvement of the primary and secondary node groups, as well as direct extension to the nodes at the level of the renal vessels.

*Channel III:* A lesser route, draining the fundus of the uterus, follows the course of the round ligament to the deep and superficial inguinal nodes.

Though there are three distinct channels, the rich anastomoses of lymphatic vessels permits no constant pattern of metastases based on the anatomical location of the cancerous growth within the uterus.

### *Node Involvement.*—

The nodes and parametria of ten cases with corporeal carcinoma were carefully dissected and studied by multiple sections. The following material is also presented in Table IV.

*Clinical Stage I*, two cases: One case with a pyometra, probably secondary to radiotherapy eleven years previously for "cervicitis," was diagnosed at autopsy. The nodes of both groups, including the inguinal nodes, were markedly enlarged. Several of the nodes exhibited fibrosis and hyalinization, a change usually attributed to extensive irradiation. The second patient died from a cerebral accident, unrelated to the malignant growth.

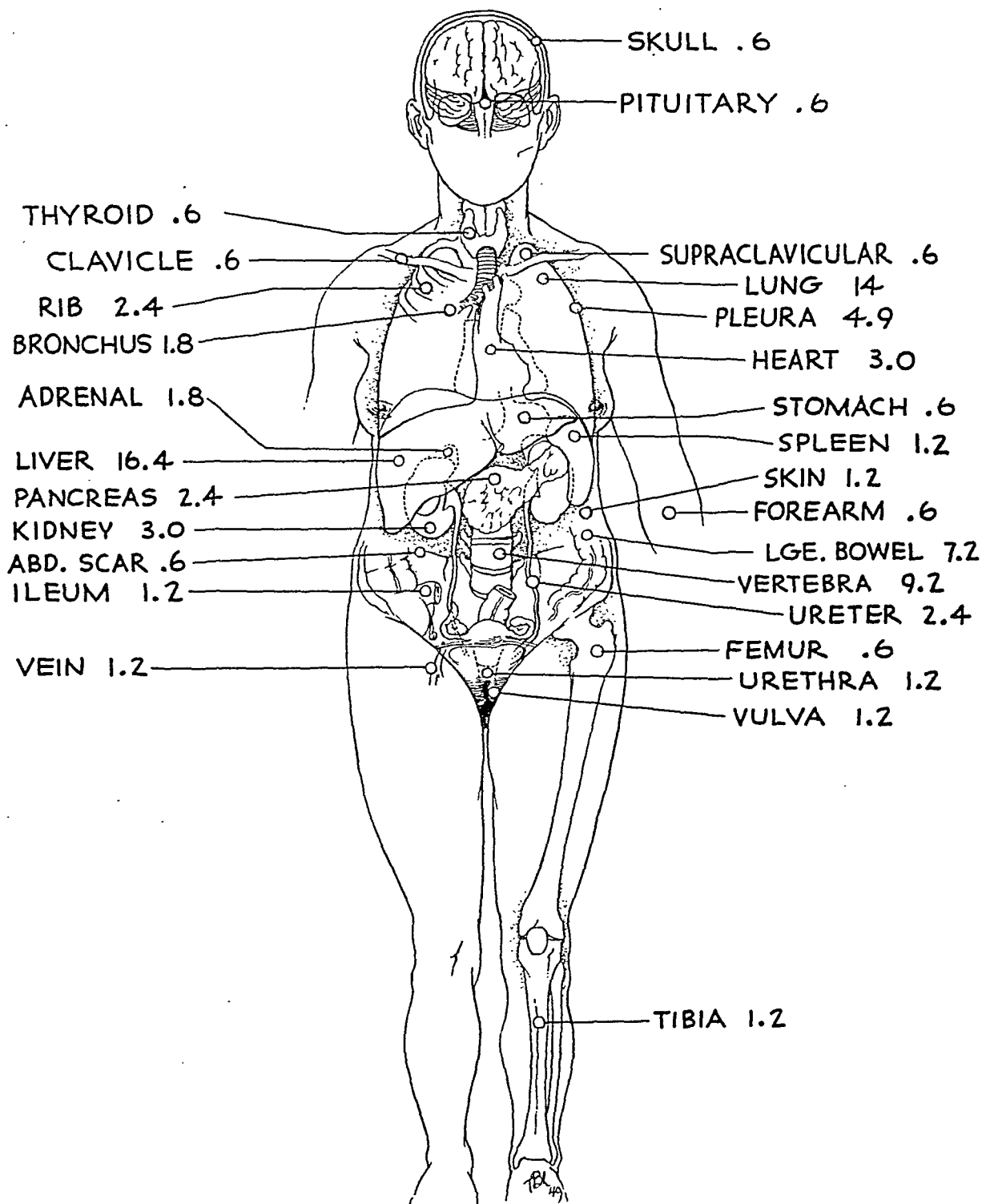


Fig. 5.—Incidence of distant metastases in 202 treated cases of cervical carcinoma.

*Clinical Stage II*, eighteen cases: One case, with the lesion in the lower uterine segment, had involvement of the parametrium, the primary and secondary groups, and distant metastases to the liver. Two of the cases had metastases limited to the secondary group of nodes. Of the five cases with the metastases limited to the nodes of the aortic group, four had distant metastases. Eight cases had various degrees of pyometra associated with generalized nonmalignant enlargement of the nodes. Whether the associated pyometra increases the tendency to metastasize is questionable, but it is a definite possibility in view of the rapid and widespread extension of the inflammatory exudate to the lymph nodes.

*Clinical Stage III*, four cases: The parametrium and primary group nodes were involved in every case. The secondary groups were involved in three of the cases. Distant metastases were present in one case.

*Clinical Stage IV*, thirty-four cases: Carcinomatous involvement of the parametrium was present in twenty-four cases. The primary nodes were sites of metastases in fifteen cases, the secondary nodes in seventeen cases. In eight cases, the metastases were limited to the nodes of the aortic group. Seventeen of the thirty-four cases had diffuse peritoneal involvement and twenty-three cases had distant metastases.

TABLE V. INCIDENCE OF NODE GROUP INVOLVEMENT IN SIXTY-FOUR CASES OF CORPOREAL CARCINOMA

	PARA-METRIUM	PRIMARY GROUP	SECONDARY GROUP	INGUINAL NODES	AORTIC NODES ONLY	PERITONEUM	DISTANT METASTASES
<i>Stage I</i> (8)	—	1	—	—	—	—	—
<i>Stage II</i> (18)	1	1	3	3	5	—	4
<i>Stage III</i> (4)	4	4	3	1	—	—	1
<i>Stage IV</i> (34)	24	15	17	7	8	17	23

The histopathological changes in some of the lymph nodes were similar to those changes usually interpreted as indication of the effects of irradiation. The relative frequency of a pyometra in association with these hypertrophic nodes increases the difficulty of the gross interpretation of their exact histopathological status. The variation in size and palpable consistency of the nodes, in the presence of corporeal carcinoma, is greater than in similar nodes of the cases with cervical carcinoma. Unfortunately, we are unprepared to present the exact percentage of difference.

The route of lymphatic spread presents a fairly consistent pattern. All three channels can be followed in some instances, but for the majority of cases the rich intercommunicating vessels within the myometrium permit a frequent selection of either main channel despite the localized anatomical site of the cancerous growth. This series emphasizes the tendency of corporeal carcinoma metastases to involve directly the nodes of the aortic chain.

Including the seventeen cases with "frozen pelvis," 46 per cent of the series had malignant involvement of the parametrium; 33 per cent of the series had metastases to the nodes of the primary group and 36.5 per cent of the secondary group. The metastases were limited to the aortic group in 20.6 per cent of the cases. Distant metastases occurred in 44.4 per cent of the series.

*Clinical Stage II*, four cases: Microscopic metastases were present in the parametria of one case where the primary lesion was confined to the upper third of the uterus. This patient died of hemorrhage. In two cases, nodes of both groups were involved. One died of pneumonia following upper abdominal surgery; the second patient died of an acute nephritis. The fourth case had a direct metastasis to the aortic group and a small metastasis in the left adrenal gland. The lesion in this case was located on the right side of the fundus of the uterus.

TABLE IV. INCIDENCE OF NODE GROUP INVOLVEMENT IN TEN CASES OF CORPOREAL CARCINOMA

	Parametrium		Paracervical		Obturator		Hypogastric		Ext. Iliac		Com. Iliac		Inguinal		Sacral	Aortic	Dist. Metas.
	RT	LT	RT	LT	RT	LT	RT	LT	RT	LT	RT	LT	RT	LT			
STAGE I (2)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
STAGE II (4)	1	1	1	-	1	1	2	2	2	1	2	1	2	1	2	1	1
STAGE III (3)	1	1	-	-	1	-	-	-	-	-	1	1	1	-	-	2	2
STAGE IV (1)	1	1	-	-	-	-	1	1	1	1	1	1	1	1	1	1	1

*Clinical Stage III*, three cases: Parametrial involvement occurred in one case with metastases to the right obturator nodes (two nodes). The primary lesion was on the posterior wall just above the internal os. The patient died from severe cachexia and hemorrhage. In one case where the original growth was on the posterior wall of the uterus, metastases were found in the common iliac, the aortic, and the inguinal groups. The patient died of uremia; the exact cause was not determined. In the third case, with the lesion on the posterior and right walls of the uterus, the metastases went directly to the aortic group. Cases 2 and 3 had, in addition, distant metastases.

*Clinical Stage IV*, one case: The serosa of the uterus was perforated, but no contiguous involvement of the adjacent bowel or peritoneum was noted. With the exception of the paracervical and the obturator nodes, all groups of nodes were involved. The patient had distant metastases to the liver, mediastinal nodes, and the pleura. Death was due to a pyelonephritis.

The incidence of node and parametrial involvement in the ten carefully studied cases of adenocarcinoma of the corpus uteri is presented in Fig. 6. The higher frequency of metastases to the nodes of the secondary group emphasizes the tendency of this type of growth to follow the main lymph channels which drain directly into the aortic nodes. Intercommunicating vessels account for the metastases to the nodes of the common iliac group. Unilateral and cross metastases are not infrequent, and do occur, regardless of the anatomical location and clinical stage of the disease.

Despite the contrary impression, local and distant metastases are not infrequent in cases of adenocarcinoma of the body of the uterus.<sup>23, 31, 32, 35</sup> The following brief comments on the observations of sixty-four cases of corporeal adenocarcinoma, studied at necropsy, are also presented in Table V.

*Clinical Stage I*, eight cases: In one case where the lesion was on the anterior wall metastases occurred in the right hypogastric group. The parametrium was microscopically free of metastases and it is possible that this unusual site represents extension along an intercommunicating vessel from the ovarian trunk. Three of these cases had a pyometra with associated, benign enlargement of the nodes. The incidence of node disintegration is less severe than the changes present in nodes affected by intensive irradiation.

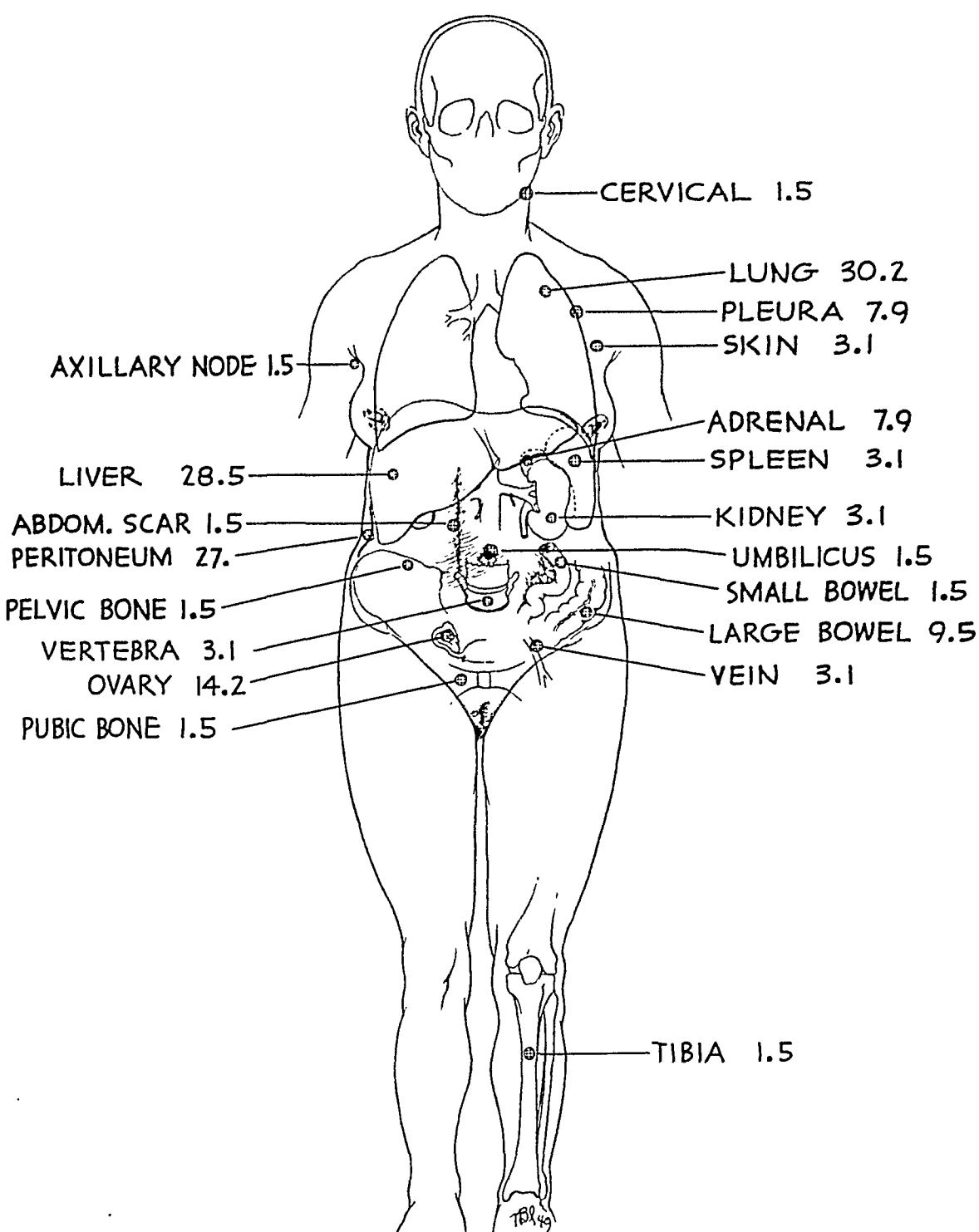


Fig. 7.—Incidence of distant metastases in sixty-four cases of corporeal carcinoma.

### Distant Metastases (Fig. 7)

Distant metastases, including the seventeen (26.9 per cent) cases with extensive carcinomatosis, were present in 44.4 per cent of the cases. The lungs, liver, ovary, bowel, pleura, adrenal gland, and the bones were the most frequent sites. The liver and the adrenal gland were the most common sites of metastases when the aortic group represented the only node involvement.

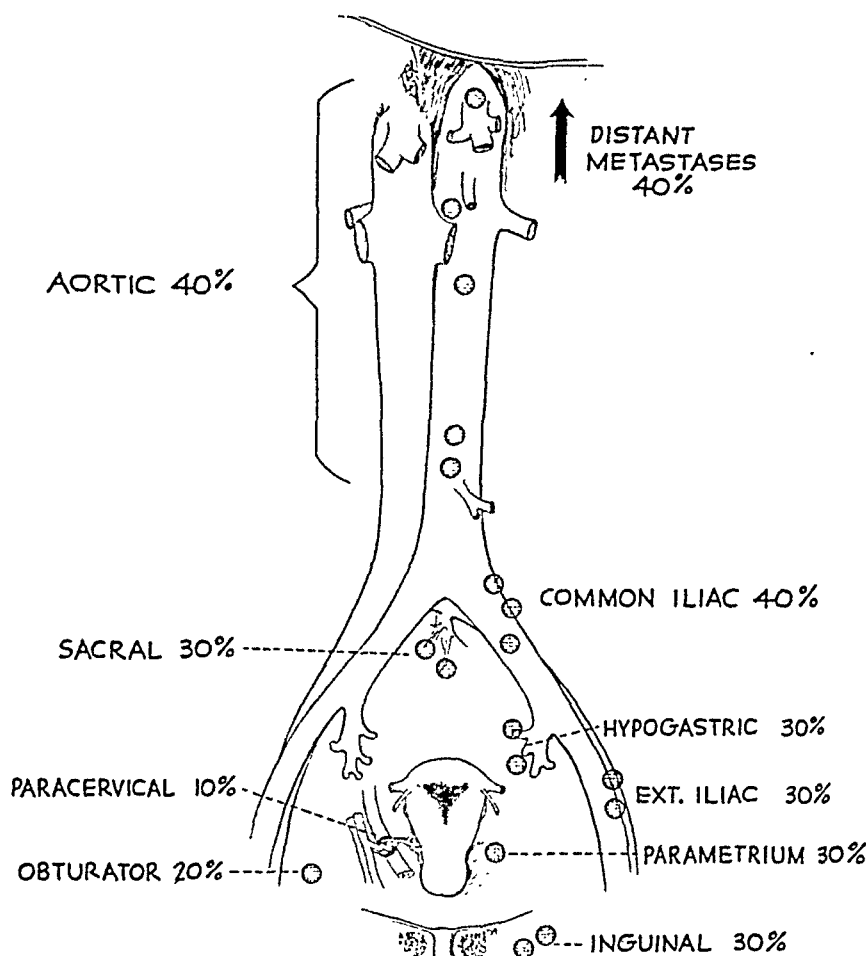


Fig. 6.—Incidence of node group involvement in ten cases of corporeal carcinoma.

### The Assigned Cause of Death<sup>31, 32</sup>

Death due to causes unrelated to the malignancy occurred in 15.8 per cent of the cases. The assigned causes of death, attributable to the corporeal carcinoma, in order of frequency, were uremia and/or pyelonephritis (25.3 per cent), hemorrhage and/or cachexia (17.4 per cent), extensive carcinomatosis (15.8 per cent), pulmonary emboli or thrombosis (14.2 per cent), and peritonitis and/or intestinal obstruction (12.6 per cent). An additional 12.6 per cent of the series had various degrees of hydroureter and hydronephrosis and 28.6 per cent of the cases had pyometra; 14.2 per cent were not diagnosed correctly until autopsy.

### Summary

1. The necropsy study of 420 cases of carcinoma of the cervix (356 cases) and the corpus uteri (64 cases) is presented with the incidence of lymph node involvement, distant metastases, and the assigned cause of death.

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### Discussion

DR. J. P. PRATT, Detroit, Mich.—The accumulation of such a wealth of material over a period of years shows a prodigious effort and faithful devotion to a worthy cause. As a result of his investigations, the author must have gained valuable impressions which would be difficult to put into words or communicate to others. The presentation of this interesting data suggests many questions relating to clinical investigation. It must have required considerable restraint not to digress.

By limitation of the subject to spread of carcinoma through the lymphatics other pathways have been excluded, namely, continuity, contiguity, and the blood vascular system. Distant metastasis (liver, lung, brain, bone) could hardly be explained by the lymphatic route alone. It seems likely that in many instances spreading occurred by more than one route and analysis of the cases so indicates. How would consideration of the other means of extension have altered the interpretation of lymphatic spread?

The reported error of approximately 20 per cent in the gross diagnosis of the lymph node status at necropsy is interesting. One could hardly expect to do as well at operation for the field of exploration is more limited. Yet it is necessary to act on one's judgment at the time, as it would be too long to wait for a pathologic report on each gland removed. This error in judging gross appearance of glands might well be used as an argument in favor of a radical operation in every case.

An error of more than 25 per cent in the clinical diagnosis of the extent of carcinoma is an important consideration. While the stages of invasion are well defined, it is often

2. Careful dissection and multiple sections of the lymph nodes in twenty-six nontreated and fifteen treated cases of cervical carcinoma emphasize the frequency of early metastasis, the probable impedimentary effect of irradiation, and traces the routes of lymphatic spread. The parametrium was involved in 77 per cent of the nontreated cases and 33 per cent of the treated cases. Distant metastasis occurred in 27 per cent of the nontreated and 53 per cent of the treated cases.

3. In the series of 356 nontreated and treated cases of cervical carcinoma, the probable arresting effect of irradiation is emphasized by the difference in the node group involvement. The incidence of distant metastases varies little in the two groups.

4. The lymphatic spread, from cervical carcinoma, follows a constant course, the parametrium, the nodes of the primary group, and finally the secondary group nodes, before extension beyond the pelvis.

5. Uremia, the end result of ureteral compression, was the assigned cause of death in 58.5 per cent of the nontreated cases and 49.3 per cent of the treated cases. Evidence of ureteral obstruction and hydronephrosis was found in 82.8 per cent of the nontreated and 78.6 per cent of the treated cases.

6. The routes of lymphatic spread of endometrial carcinoma are less constant. The three main channels permit involvement of the same node groups as found in cervical carcinoma, or a by-passing of the primary groups with metastases directly to the inguinal nodes or the aortic nodes.

7. Uremia and/or pyelonephritis was the most frequent assigned cause of death in cases with endometrial carcinoma.

8. The disintegrating effects of irradiation does not occur in all of the treated cases, and similar changes, though usually of a lesser degree, are present in the nontreated cases. Histopathological changes are more frequent when there is a history of infection.

9. Histopathological evidence is lacking to support the claim that metastatic nodes may be sterilized by irradiation. The necropsy findings suggest the possibility of this effect.

10. The numerous intercommunicating lymphatic vessels account for the unpredictable sites of metastases.

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involved from carcinoma of the endometrium. Therefore, I think if we are to do surgery we must take the same attitude in carcinoma of the endometrium as we do in carcinoma of the cervix.

At this moment we are caught in a dilemma. Years ago we did a few radical operations for carcinoma of the cervix but we did not have suitable equipment and we had a desperate time. The treatment shifted to radium and x-ray and, recently, back to surgery. We lacked ability to recognize the importance of the surgical approach and there was a lack of knowledge of irradiation reactions. Eventually I think we will land in a position where we can say "this patient should be operated upon and this one deserves a decent amount of irradiation." Our problem is to select with good reason those cases which should be operated upon and those which should be irradiated, and this applies equally to carcinoma of the endometrium as it does to carcinoma of the cervix.

DR. CHARLES A. BEHNEY, Philadelphia, Pa.—Dr. Henriksen's careful study and excellent presentation are a great addition to our understanding of the spread of pelvic cancer. In a somewhat similar investigation of 166 patients who had died of cancer of the cervix, we regarded all extrapelvic lesions as metastatic because we could not distinguish between pelvic metastasis and extension by contiguity. We classified our cases of metastases as abdominal, thoracic, and skeletal, and these correspond to the author's "distant metastases." The distance from the primary tumor to the most remote point at which metastasis will be discovered is influenced by the cellular characteristics of the neoplasm and the time the patient survived after the onset of her disease. In our cases, metastases beyond the pelvis occurred in proportion to the anaplasticity of the tumor cells. Extension of carcinoma of the cervix via lymphatics is not unlike invasion of drain pipes by roots. If the incurable patient lives long enough, permeation will continue to distant regions.

DR. HENRIKSEN (Closing).—Both the clinical and pathological evidence points to the fact that metastases travel by the blood stream as well as by the lymphatics. However, to follow the vascular pathways would require years of study far beyond our facilities. We, therefore, confined this study to the routes of lymphatic spread and have listed the sites of the distant metastases without determining their itinerary. Invasion by direct extension is also a very important method of cancerous spread.

Of the thirty-two cases of carcinoma of the cervical stump, it is assumed that three of the cases were present at the time of surgery as they were found within six months following the subtotal hysterectomy.

The problem of the clinical interpretation of persistent or recurrent postirradiation parametrial induration remains unanswered. From observations at necropsy we do not subscribe to the tenet that asymmetrical or nodular induration is pathognomonic of residual or recurrent carcinoma. Another disturbing fact is that not infrequently a palpably normal parametrium contains lymph channels loaded with cancer.

Occasionally distant metastases are found in the treated cases with no demonstrable evidence of local activity. A careful study of the nodes of the primary and secondary groups will usually reveal nests of cancer cells within thickened lymph nodes. The gross findings in such cases are of little value.

Regarding the causes of ureteral obstruction in the treated cases, compression by either the residual or recurrent tumor growth is the most frequent finding; however, in this series, 2.2 per cent of the cases showed actual invasion and perforation of the ureteral wall. Irradiation may also affect the ureter causing an actual constriction or in the occasional case, a sloughing of the ureteral wall.

difficult to place the lesion in the correct stage by clinical examination. Apparent cures of extensive lesions by radiotherapy may be open to question as to the diagnosis of the stage that was treated. Those who combine operation with radiotherapy will recall instances of an error in diagnosis as to the extent of the lesion.

The source of error varies, as is indicated in the following three examples: A patient with carcinoma of the cervix had an apparent extension into the left broad ligament. Radiotherapy appeared to shrink the cervical growth but the lesion in the broad ligament remained. When the uterus was removed at operation no vestige of malignancy remained in the cervix and the mass in the broad ligament proved to be endometriosis. A second patient had a carcinoma of the cervix and extensive induration in the broad ligament which preoperatively was thought to be malignant. After radiotherapy the induration in the pelvis improved. At operation the mass in the ligament proved to be due to a mixed infection. A third patient had clinical findings similar to the second patient. In this instance the induration of the broad ligament was part of a tuberculous peritonitis. In these instances the carcinoma of the cervix was in reality only Stage I or II at the most; they might well have been classed as Stage III or IV by clinical examination.

Carcinoma of the cervical stump as mentioned in thirty-two cases, i.e., more than 8 per cent, is a conspicuous occurrence. Do the records show whether the growth was present in the stump at the time the fundus was removed?

Extensive fibrosis of the parametrium was noted as an effect of irradiation. I have frequently been puzzled about the interpretation of induration in the pelvis at the time of follow-up examination. It has been assumed that symmetrical induration is probably an irradiation effect, while asymmetrical or nodular induration probably represents a recurrence of growth. Would the necropsy findings support this assumption?

Were there any distant metastases in treated patients who had no local recurrence in the pelvis? I had one patient with metastasis to the humerus discovered eight years after treatment. There were no recurrences in the pelvis.

Ureteral obstruction is an important item. Was it due to recurrence, invasion, or constriction by scar tissue? Parametrial involvement was reported in 77 per cent of the nontreated cases and only 33 per cent of the treated cases, but ureteral obstruction was nearly as common for the treated (78.6 per cent) as for the untreated (82.8 per cent). Should one infer that damage from irradiation is a cause of ureteral obstructions?

An important lesson to be learned from the material presented is the necessity of caution in comparison of statistics. Even at necropsy there was an error of 20 per cent in the interpretation of the gross appearance and 25 per cent in clinical diagnosis of the extent of the lesion. At best, statistical statements can only be relative.

DR. JOE V. MEIGS, Boston, Mass.—I feel very sure, at least I think I am right, that when a decision is finally made as to whether these patients should be operated upon or irradiated, according to their response to irradiation, that those who are irradiated but are radiation-resistant and do not respond well and die of the disease, will have very little involvement of the urinary tract. But in those who are sensitive and are given large doses and whom we hope to cure, we will cure the local disease but there will be involvement of the urinary tract. That is something we must find out about, irradiation sensitivity versus irradiation resistance. If Dr. Everett's analysis is accurate, we will find ureteral involvement due to irradiation in the sensitive patients and those patients who are free of this complication and are radiation-resistant will die of progression of the disease.

With reference to Dr. Henriksen's paper: In patients with carcinoma of the cervix we do a combination of the Wertheim operation and the Taussig operation; in other words, a radical hysterectomy with bilateral dissection of the pelvic lymph nodes. I am sure that in some cases I have not gone high enough and in some cases I am equally sure that I have not gone low enough. I think that is important.

This is true and important: in our usual operation for carcinoma of the endometrium we do a radical total hysterectomy but we do not routinely resect the lymph nodes. To my surprise, in one patient in whom I did a radical operation there were positive lymph nodes in the external iliac region. Dr. Henriksen's figures show you definitely where areas are

The decision to call a particular papillary serous cyst benign or borderline is often difficult to make and inconsistency in this respect undoubtedly further explains the great variation in end results presented from different parts of the country.<sup>27-29</sup> It is most unlikely that surgical and radiation techniques in various parts of the country are so much different that they would produce this wide range of results.

TABLE I. STATISTICS OF VARIOUS AUTHORS, FIVE-YEAR CURE RATES IN CANCER OF THE OVARY

AUTHOR	YEAR	NUMBER OF CASES	FIVE-YEAR CURE RATE (PER CENT)
Straussman	1921	17†	8.5
Schafer	1922	70*	13.0
Ford	1928	59†	28.8
May	1930	†	31.0
von Peham and Amreich	1930	115*	9.5
Heyman	1932	134†	31.3
Anspach	1934	24	29.1
Norris	1934	44	50.0
Harris and Payne	1935	51*	51.0
Murphy	1935	92†	24.0
Lynch	1936	64	35.5
Jacobs and Stenstrom	1937	31	35.4
Counseller	1940	143*	65.4
		118†	50.5
		36‡	16.7
Meigs	1940	154	15.5
Pemberton	1940	114	32.0
Jones	1941	30	23.3
Walter, Bachman, and Harris	1941	63*	6.3
		61†	22.9
Taylor and Greeley	1942	138	15.2
Helsel	1946	100	20.0
Campbell and Singman	1947	69	13.0
Swinton and Yancey	1947	45	14.0
Munnell and Taylor	1949	200	27.5

\*Surgery alone.

†Surgery and x-ray.

‡X-ray alone.

TABLE II. THE FIVE-YEAR END RESULTS OF 200 PRIMARY CASES OF CARCINOMA OF THE OVARY (Sloane Hospital for Women, 1922 Through 1943)

HISTOLOGIC TYPE	A  TOTAL CASES	B		C  DETER- MINATE REMAIN- DER A-B	D  TOTAL FIVE- YEAR CURES	RELATIVE FIVE- YEAR CURE RATE D/C (PER CENT)	ABSO- LUTE FIVE- YEAR CURE RATE D/A (PER CENT)
		INDETERMINATE					
		WELL WHEN LOST	DIED OF OTHER CAUSES				
Papillary serous cystadenocarcinoma	125	18	1	106	38	35.8	30.4
Undifferentiated papillary adeno- carcinoma	22	-	-	22	0	0	0
Papillary pseudo- mucinous cystadeno- carcinoma	15	1	-	14	9	64.2	60.0
Granulosa cell tumor	13	2	-	11	7	63.6	53.8
Dysgerminoma	3	-	-	3	1	33.3	33.3
Unclassifiable	10	-	-	10	0	0	0
Clinical diagnosis (no operation)	12	-	-	12	0	0	0
Over-all Totals	200	21	1	178	55	30.8	27.5

## OVARIAN CARCINOMA\*

### A Review of 200 Primary and 51 Secondary Cases

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PROGRESS in improving the survival rate from cancer of the ovary in the past two or three decades has been relatively slight. The insidious onset of the disease frequently results in its early stages going unrecognized by the patient; it is also often unrecognized as such by the doctor. The site of the lesion renders it inaccessible to simple methods of anatomical diagnosis such as smears, biopsy, and curettage, as in the case of cervix and corpus uteri tumors. It is fortunately not a very common type of genital cancer, occurring next after cervix and fundus in frequency of carcinomas of the female genitals.<sup>14</sup>

#### I. Material and Method of Study

During the period 1922 through 1943 there were 200 cases of primary ovarian carcinoma of the ovary seen at the Sloane Hospital for Women. Both service and private patients are included in this number. There also were fifty-one cases of recurrent or metastatic (secondary) ovarian carcinoma seen during this period. This presentation is concerned only with the primary group and the secondary group will be but briefly mentioned.

The microscopic specimens of these 200 cases were all re-examined so that we should have a comprehensive approach to the study. This was done along with examination of all the benign papillary tumors that occurred during this same period. Some reclassification inevitably resulted, with the inclusion of one or two tumors not previously called malignant. At the same time the papillary carcinomas were graded according to degree of histological malignancy. This grading involves only the papillary serous group in so far as discussion of end results is concerned since the pseudomucinous group was too small to be statistically significant if broken down into subgroups.

Unless otherwise mentioned, all reference hereafter will be to the group of 200 primary cases.

#### II. End Results of 200 Cases of Primary Ovarian Cancer

A review of the literature reveals a marked inconsistency in the five-year survival rates of previous investigators. Table I presents a summary of the five-year cure rates of others in cancer of the ovary. The wide range of reported cure rates is most striking. The explanation for this variation undoubtedly lies in the criteria for making a pathological diagnosis of carcinoma of the ovary. Some investigators<sup>8</sup> feel that any papillary tumor of the ovary is malignant.

\*Presented in condensed form at the Seventy-Second Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 16 to 18, 1949.

### III. End Results of Fifty-One Cases of Secondary Ovarian Cancer

The five-year end results of fifty-one cases of recurrent or metastatic ovarian carcinoma are presented in Table III. There were no five-year survivors of the three patients with recurrent ovarian cancer or of the eighteen cases of ovarian carcinoma metastatic from the stomach or colon. The twenty-eight cases of carcinoma of the ovary metastatic from the fundus uteri include those with both gross or microscopic metastases; nine of these lived five or more years after treatment was instituted. There was only one case of adenocarcinoma metastatic from the breast and one case of a melanosaercoma metastatic from the eye; neither survived.

TABLE III. FIVE-YEAR END RESULTS. RECURRENT AND SECONDARY OVARIAN CARCINOMA

PRIMARY SITE	TOTAL CASES	RELATIVE FIVE-YEAR CURE RATE	ABSOLUTE FIVE-YEAR CURE RATE
Recurrent	3	0	0
Stomach and colon	18	0	0
Fundus	28	(9) 37.5%	32.1%
Eye	1	0	0
Breast	1	0	0

No further reference to this secondary group will be made.

### IV. Factors Determining Prognosis

#### A. Histogenetic Type of Tumor.—

The importance of the histological type of tumor encountered in determining prognosis is evident from examining comparative cure rates in Table II and Fig. 1.

#### B. Histological Degree of Malignancy.—

The importance of the histological degree of malignancy in relation to the five-year survival rate is most apparent in the 125 cases of papillary serous cystadenocarcinoma which made up the bulk of the series. In the course of re-examining and classifying the histological specimens of the 200 primary cases they were graded according to histological degree of malignancy. The papillary serous carcinomas were divided into four grades: borderline, Grade I, Grade II and Grade III, in order of progressively greater degrees of malignancy.

TABLE IV. THE END RESULTS OF 125 CASES OF PAPILLARY SEROUS CYSTADENOCARCINOMA ACCORDING TO HISTOLOGICAL GRADE OF MALIGNANCY (Sloane Hospital for Women, 1922 through 1943)

HISTOLOGICAL GRADE OF MALIGNANCY	A  TOTAL CASES	B INDETERMINATE		C  DETER- MINATE REMAIN- DER A-B	D  TOTAL FIVE- YEAR CURES	RELATIVE FIVE- YEAR CURE RATE D/C (PER CENT)	ABSOLUTE FIVE- YEAR CURE RATE D/A (PER CENT)
		WELL WHEN LOST	DIED OF OTHER CAUSES				
Borderline	28	8	1	19	17	89.8	60.7
Grade I	29	6	0	23	14	60.8	48.2
Grade II	19	1	0	18	4	22.2	21.0
Grade III	49	3	0	46	3	6.5	6.1
Group Total	125	18	1	106	38	35.8	30.4

Table IV presents the five-year survival rates for this group of papillary serous cystadenocarcinomas and very clearly shows the direct relationship between

The five-year end results of the 200 cases of primary carcinoma of the ovary seen at Sloane Hospital for Women in the period 1922 through 1943 are presented in Table II. Two different survival or cure rates are given, the relative and the absolute. The absolute survival rate is based upon the total number of patients seen. The relative survival rate is derived from the "determinate" cases, that is, by excluding patients who died of other disease or who were lost to follow-up but well at the time they were lost. In this determinate group those who had residual or recurrent disease at the time they were lost are considered dead of cancer.

The over-all relative five-year survival rate for the 200 cases was 30.8 per cent and the absolute rate was 27.5 per cent. Papillary pseudomucinous cystadenocarcinoma and granulosa cell tumors were the two most favorable types with relative cure rates for each being above 60 per cent. No five-year survivals resulted in those patients with undifferentiated adenocarcinoma, unclassifiable carcinoma or those who were not operated upon. Almost two-thirds of the total group were patients with papillary serous cystadenocarcinoma; the five-year survival rates for this group are close to the over-all figures, being 35.8 per cent relative and 30.4 per cent absolute.

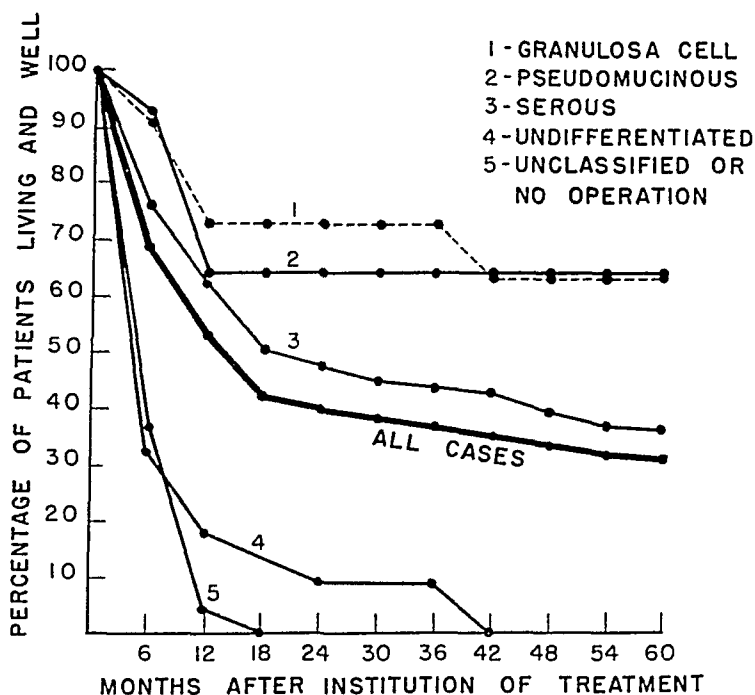


Fig. 1.—Five-year survival curves in carcinoma of the ovary according to histological type.

Points on a five-year survival curve of the determinate cases were calculated for each six months following treatment and the results are shown in Fig. 1.\* It will be noted that at the end of one and a half years almost 60 per cent of the patients had died and that thereafter the curve drops much more slowly so that at the end of five years' time it has dropped only another 10 or 12 per cent. This extensive loss of life within the first year and a half after treatment is begun testifies to the malignancy of this type of genital cancer.

\*Attention should be called to the theoretical and practical advantage of survival curves of the type shown in Fig. 1. Such curves can be used as a baseline for the evaluation of a new type of treatment over the old in different types of cancer before five years have elapsed. Obviously, the number of cases involved must be of statistical significance.



Fig. 3.—Bilateral ovarian cysts treated by bilateral salpingo-oophorectomy. Original pathological diagnosis was papillary serous cystadenomas. This picture is of the original tumor.

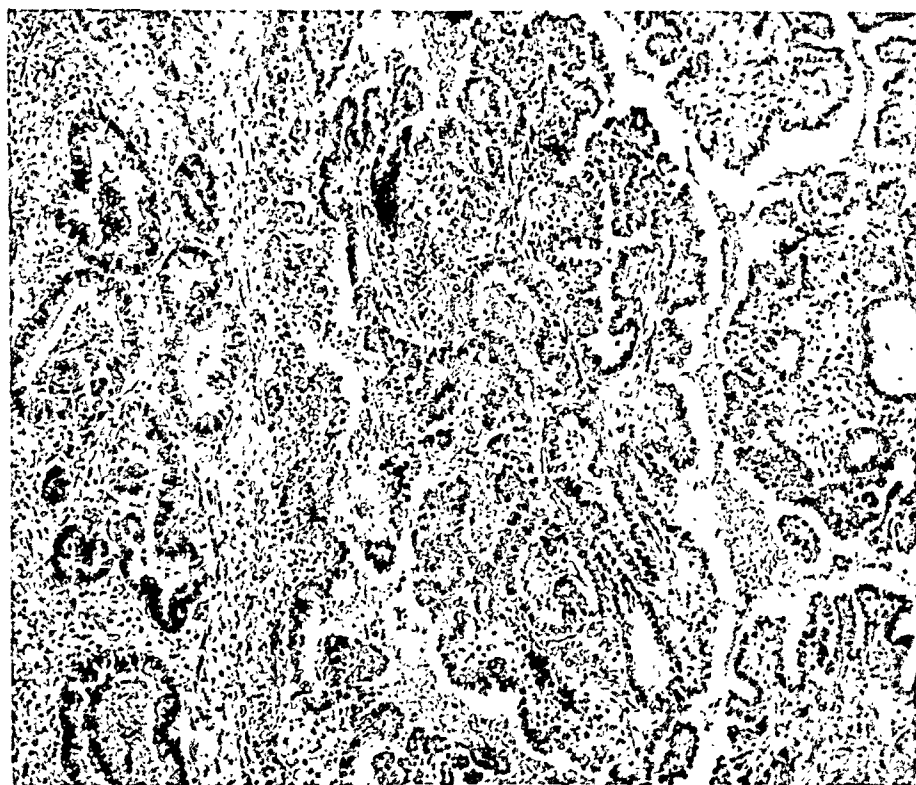


Fig. 4.—Same patient as shown in Fig. 3. Showing the recurrence twelve years later. Now called a low-grade papillary serous cystadenocarcinoma.

histological degree of malignancy and end results. The borderline group provided the highest percentage of five-year survivors, 89.8 per cent relative and 60.7 per cent absolute. There was a progressive and rapid decrease in the next three groups, 48.2 per cent for Grade I, 21.0 per cent for Grade II, and 6.1 per cent for Grade III. Fig. 2 presents the five-year survival curves for this group.

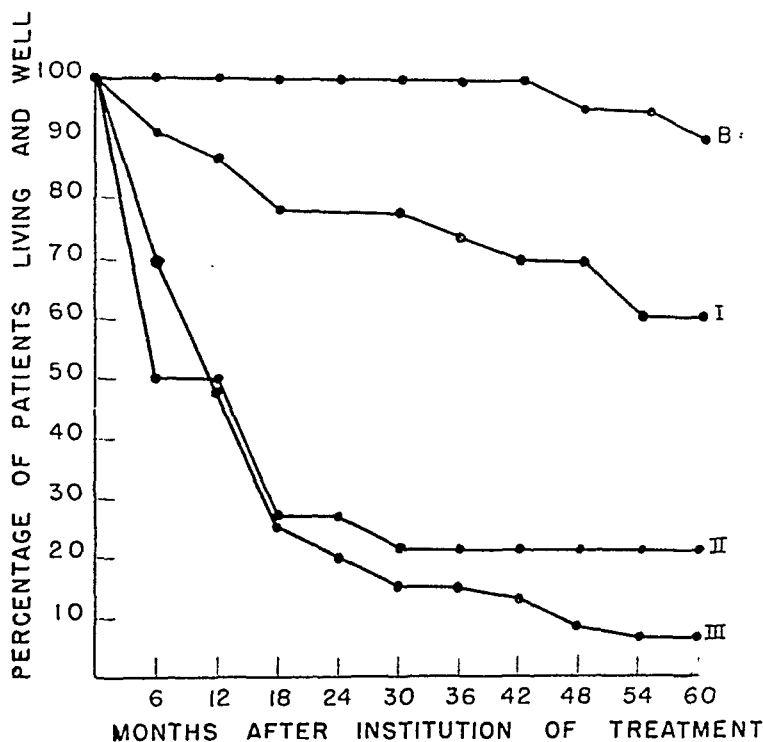


Fig. 2.—Five-year survival curves for papillary serous cystadenocarcinoma according to degree of histological malignancy.

Although the use of the term "borderline" suggests that there is some question as to whether or not the tumor is properly called cancer, it is our belief that this group is truly malignant. The "borderline" papillary serous cystadenocarcinoma has long presented the pathologist with difficulty in making this decision. By virtue of the fact that there were included in this group of twenty-eight "borderline" cases those of a fairly uniform histological appearance, and since there were two five-year failures among the nineteen traced cases, it follows that the remaining seventeen successfully treated cases represented true carcinomas. Further support to this impression is gained from the fact that there were three failures *after* five years in this group; further mention will be made of these three cases later. Briefly, the criteria for placing a papillary serous tumor in this borderline group include: (1) some degree of cellular anaplasia, (2) excessive papillary formation, (3) invasion of the stroma by adenomatous elements, and (4) some piling up of the epithelium. Figs. 3 and 4 are photomicrographs of a case of borderline papillary serous cystadenocarcinoma showing some of these characteristics.

#### C. Clinical Extent of Disease.—

The 200 primary cases were divided into four clinical stages according to extent of cancer as determined at operation. Clinical Stage I includes those cases with involvement of one ovary alone; Stage II includes those with both ovaries involved; Stage III includes those with one or both ovaries involved together with spread to pelvic peritoneum or viscera (Fallopian tubes excluded);



Of the nine survivors of five years or more in clinical Stages III and IV all but one were of low-grade histological malignancy. Four were borderline serous carcinomas, two were Grade I serous carcinomas, two were pseudomucinous carcinomas and only one was a Grade III serous carcinoma (Table VI).

Clinical extent of disease is considerably dependent upon the histological type and degree of histological malignancy. The tumors of high-grade malignancy are more frequently found to have spread outside the ovaries by the time the patient comes to operation.

## V. Management

Some type of surgery was carried out in 188 of the 200 cases. This ranged from exploratory laparotomy to complete removal of the internal genitalia. Surgery remains the fundamental part of the treatment of carcinoma of the ovary.

### A. Surgical Management of the Unilateral Ovarian Carcinoma.—

Of considerable interest, albeit confusing, is Table VII showing the five-year survival rates in patients with *unilateral* ovarian carcinoma. Of forty-six patients with only one ovary malignant, one-half had radical surgery performed (bilateral salpingo-oophorectomy and hysterectomy) and one-half had conservative surgery performed (conservation of the uninvolved ovary with or without conservation of the uterus). The five-year survival rates for the two groups are essentially the same, a fact mentioned by previous investigators.<sup>17</sup> None of these conservatively treated patients was reoperated upon and only nine of them received postoperative x-ray therapy. Two patients, both with unilateral pseudomucinous carcinomas, subsequently had normal pregnancies.

TABLE VII. RELATION OF TYPE OF SURGERY TO FIVE-YEAR CURE RATE IN CLINICAL GROUP I CASES  
(One Ovary Alone Involved)

HISTOLOGICAL TYPE	CONSERVATIVE SURGERY			RADICAL SURGERY		
	TOTAL NUMBER TREATED	FIVE-YEAR CURES		TOTAL NUMBER TREATED	FIVE-YEAR CURES	
		NUMBER	PER CENT		NUMBER	PER CENT
Papillary serous carcinoma						
Borderline	2	2	100	2	2	100
Grade I	4	3	75	2	2	100
Grade II	2	1	50	3	3	100
Grade III	6	1	17	7	1	14
Pseudomucinous carcinoma	3	3	100	6	4	67
Granulosa cell	6	4	67	3	3	100
Totals	23	14	61	23	15	65

In spite of these results which seem to indicate that unilateral oophorectomy is adequate treatment for a unilateral ovarian carcinoma that has spread no further, we cannot subscribe to a policy of conservatism in treating such cases. To the contrary, it appears probable that some of the failures in the unilateral oophorectomy group were due to preservation of the apparently sound ovary and had bilateral oophorectomy been the rule for the one-sided tumors, the results in Stage I cases might have been as good as for Stage II. Further, there were a few cases included in this series of 200 patients in whom radical surgery was carried out for what was thought to be a unilateral tumor but in whom histological examination of the apparently normal ovary revealed microscopic carcinoma. Had these few cases of gross carcinoma in one ovary and

Stage IV includes those with involvement of ovaries and pelvis with spread to the upper abdominal peritoneum or viscera. As shown in Tables V and VI the best five-year survival rates are obtained when there has been no spread beyond the ovaries. Whether ovarian involvement is unilateral or bilateral does not seem important in prognosis. As a matter of fact, the Stage II results are superior to the Stage I results but this is probably a statistical accident. What is important is the matter of localization of tumor to the ovaries. As soon as spread outside the ovaries occurs, the chances for five-year survival drop precipitously.

TABLE V. END RESULTS OF OVARIAN CARCINOMA RELATED TO EXTENT OF DISEASE  
(Based on Determinate Cases Only)  
(Sloane Hospital 1922-1943)

CLINICAL STAGES	TOTAL CASES	FIVE-YEAR CURES	
		NUMBER	PER CENT
Stage I	51	30	59
One ovary only involved			
Stage II	20	16	80
Both ovaries involved			
Stage III	25	5	20
Extension to pelvic peritoneum and/or pelvic viscera			
Stage IV	82	4	5
Extension to abdominal peritoneum and/or viscera			
Totals	178	55	27.5

TABLE VI. FIVE-YEAR CURE RATE IN OVARIAN CARCINOMA RELATED TO EXTENT OF DISEASE  
(DETERMINE GROUP ONLY)

HISTO- LOGICAL TYPE	I			II			III			IV		
	TOTAL CASES	FIVE-YEAR CURES		TOTAL CASES	FIVE-YEAR CURES		TOTAL CASES	FIVE-YEAR CURES		TOTAL CASES	FIVE-YEAR CURES	
		NUM- BER	PER CENT		NUM- BER	PER CENT		NUM- BER	PER CENT		NUM- BER	PER CENT
Papillary serous cystadeno- carcinoma												
Borderline	4	4	100	9	9	100	4	3	75	2	1	50
Grade I	6	5	83	8	7	87	5	1	20	4	1	25
Grade II	5	4	90	2	0	0	2	0	0	9	0	0
Grade III	13	2	15	1	0	0	6	1	16	26	0	0
Undifferen- tiated papillary adeno- carcinoma	3	0	0	0	0	0	3	0	0	16	0	0
Papillary pseudo- mucinous cystadeno- carcinoma	9	7	78	0	-	-	2	0	0	3	2	67
Granulosa cell tumor	9	7	78	0	-	-	1	0	0	1	0	0
Dysgermin- oma	1	1	100	0	-	-	0	-	-	2	0	0
Unclassi- fiable	1	0	0	0	-	-	2	0	0	7	0	0
Clinical diagnosis	0	-	-	0	-	-	0	-	-	12	0	0
Totals	51	30	58.8	20	16	80	25	5	20	82	4	4.8

grade malignancy limited to the ovaries. In localized tumors of higher degrees of malignancy its value is questionable except perhaps from the palliative point of view.

Certainly radiation therapy should not be withheld from the apparently hopeless case for in two cases in this series it converted inoperable cases into operable ones. Both patients had papillary serous cystadenocarcinoma, were explored and found to be inoperable, given x-ray therapy and operated upon again (one a year later, the other two years later) when clinical examination indicated a favorable change had occurred. One patient is living and well after fifteen years; the other died after four years, possibly of another disease.

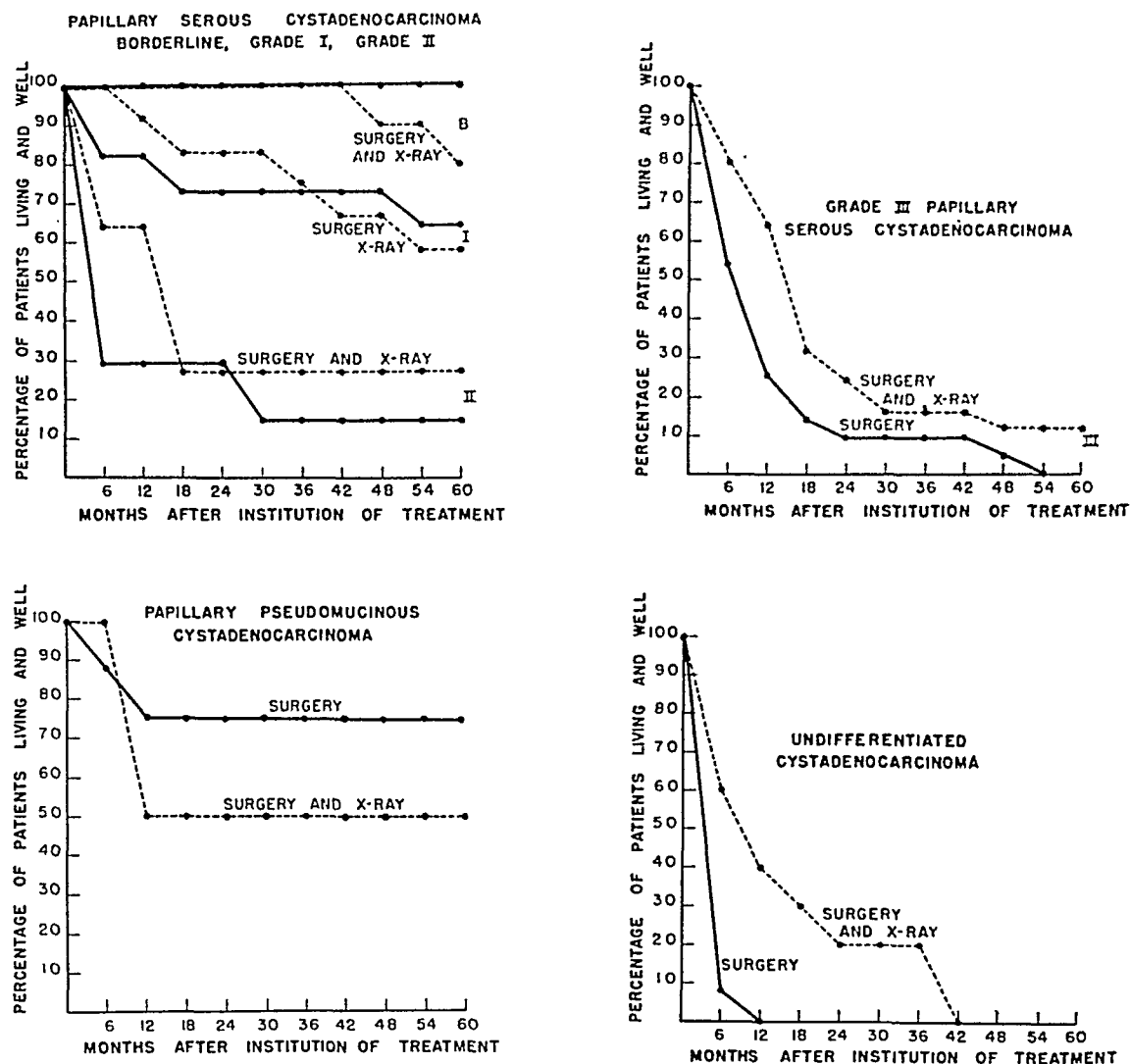


Fig. 5.—Survival curves—histological malignancy and method of treatment.

## VI. Granulosa Cell Tumors

There were thirteen granulosa cell tumors seen during this period and included in this series. Their inclusion increases the five-year survival rate by about 5 per cent since it is a tumor generally of low-grade malignancy. Only two patients received postoperative x-ray therapy and both died. There were only seven successfully treated cases in this group. This is a recurrence rate of 36 per cent, as compared with that of 28.0 per cent of Novak and Brawner.<sup>23</sup>

microscopic carcinoma in the other ovary been treated conservatively, they would undoubtedly have significantly lowered the survival rate of the conservatively treated group.

We agree with the principles of Meigs<sup>16</sup> and others, that radical surgery be performed if the tumor is papillary except in rare instances where perhaps the patient is young and childless. Here, if the gross appearance of the tumor suggests one of low-grade malignancy and if the opposite ovary seems perfectly normal, the latter and the uterus may be retained.

We cannot confirm or refute Meigs' belief in the *necessity* for total rather than subtotal hysterectomy since most hysterectomies in this series were subtotal. However, as a general rule, total hysterectomy should always be the preferred routine procedure if for no other reason than to prevent the subsequent development of carcinoma of the cervical stump.

### *B. Postoperative X-ray Therapy.—*

The value of postoperative radiation has been the subject of considerable discussion in the literature on ovarian carcinoma with wide divergence of opinion as to its value. The radiation therapists champion its use both as a palliative and curative agent.<sup>2, 5, 7, 10, 12, 15, 16, 19, 25</sup> Most gynecologists have no real conviction as to its therapeutic value<sup>3, 11, 14</sup> while a few have considered it to be not only of no value but actually injurious.<sup>6, 20</sup>

Five-year survival curves of the determinate cases treated with surgery alone and surgery plus x-ray according to histological type and degree of malignancy and according to extent of disease are shown in Figs. 5 and 6. The two factors, histological type and degree of malignancy and clinical extent of disease, should be considered jointly in attempting to determine the value of irradiation therapy as an adjunct to surgery in different situations.

In cases of tumors of low-grade malignancy such as borderline and Grade I papillary serous cystadenocarcinomas the survival curves for surgery alone are better than those for surgery plus x-ray. However, this does not mean that x-ray therapy was the cause of the poorer results in the surgery plus x-ray group; the actual reason for the poorer result in surgery plus x-ray treatment of the borderline and Grade I serous cases was that the failures, with one exception, were patients with such extensive spread of disease that they were in clinical Stages III and IV. The same explanation holds for the poorer results from surgery and x-ray in the papillary pseudomucinous cystadenocarcinoma group.

On the other hand, the survival curves for the surgery plus x-ray cases in the more malignant histological type of tumors, the Grades II and III serous carcinomas, and the undifferentiated and unclassifiable carcinomas, are better than the survival curves for surgery alone. This is probably a true picture although not a very bright one considering how very low the five-year survival results for these tumors are. Nevertheless, the only five-year survivors in the Grade III serous cases were those who received postoperative radiation. In the undifferentiated adenocarcinomas, although not curative, radiation therapy certainly seemed to prolong life, providing a moderate palliative effect.

In the survival curves based on clinical extent of disease, the superior results from surgery alone in the clinical Stages I and II do not indicate that supplementary x-ray is harmful but they do make its value very questionable. In the more widespread clinical stages of disease, Stages III and IV, postoperative x-ray therapy increased life survival time.

It would appear from this series that postoperative x-ray therapy is of value in some instances and not in others. Its value seems definite in all cases of extensive spread, clinical Stages III and IV, at least from a palliative, and occasionally from a curative, point of view. It is of no value in tumors of low-

line or Grade I malignancy. One-half of these had originally had conservative surgery for localized cancer; later recurrence in these three cases is further evidence in support of the principle of radical surgery. Three others had extensive disease, but of low-grade malignancy and received postoperative x-ray so that they lived for many years in spite of not having had complete removal of the tumor. Time of recurrence or death is shown in Table VIII.

### Discussion

Carcinoma of the ovary is still one of the least curable cancers of the female genitals. In this series 64 per cent of the patients had gross evidence of peritoneal or visceral metastases at the time of operation; in the absence of gross metastases microscopic transperitoneal or lymphatic metastases may have already occurred. Early diagnosis has been stressed as the most important means available at the present time for improving the survival rate. Lynch<sup>13</sup> has shown a correlation of duration of symptoms with survival. The present-day program of cancer education emanating from both lay and professional sources with an ever-increasing number of women presenting themselves periodically for routine examination should certainly increase the number of early diagnoses. Whether or not this is going to effect ovarian cancer survival appreciably remains to be seen. Twombly<sup>30</sup> reports that out of forty patients in whom ovarian cancer was discovered prior to the onset of symptoms (i.e., found on routine examination for other causes or developing while under observation at the Memorial Hospital), *none* survived five years and 50 per cent were dead within nine months. Certainly an inescapable fatalistic conclusion comes from our own series which shows so clearly the importance of the histological type of tumor and the histological degree of malignancy in determining prognosis. The future must offer more than early clinical diagnosis if ovarian cancer survival is to be materially increased. Perhaps this will be a method affording early histological or cytological diagnosis that will precede clinical signs; perhaps it will be higher voltage x-ray or improved methods of administering radiation.

### Summary

1. Two hundred cases of primary carcinoma of the ovary with at least five-year follow-up are presented. The papillary serous cystadenocarcinomas make up almost two-thirds of the total series.
2. The five-year over-all survival rates are 30.8 per cent absolute and 27.5 per cent relative.
3. The so-called borderline papillary serous cystadenocarcinoma is a malignant tumor.
4. Prognosis depends chiefly upon the histogenetic type of tumor and upon the histological degree of malignancy, both of which largely control the clinical extent of disease. Ovarian tumors of low-grade histological malignancy have the most favorable prognosis. Similarly, tumors still confined to the adnexa are most favorable to treat. Clinical extent of disease is usually greater in tumors of high-grade histological malignancy.
5. The following tumors are regarded as being of low-grade histological malignancy; papillary serous cystadenocarcinoma, borderline and Grade I;

TABLE VIII. RECURRENCE AND/OR DEATH AFTER FIVE YEARS

HISTOLOGICAL TYPE	YEAR									TOTAL DEATHS AFTER FIVE YEARS
	6	7	8	9	10	11	12	13	14	
Papillary serous cystadeno- carcinoma										
Borderline	1		1						1	3
Grade I				1		1	1			3
Grade III		1								1
Pseudomucinous cystadeno- carcinoma	1									1
										8

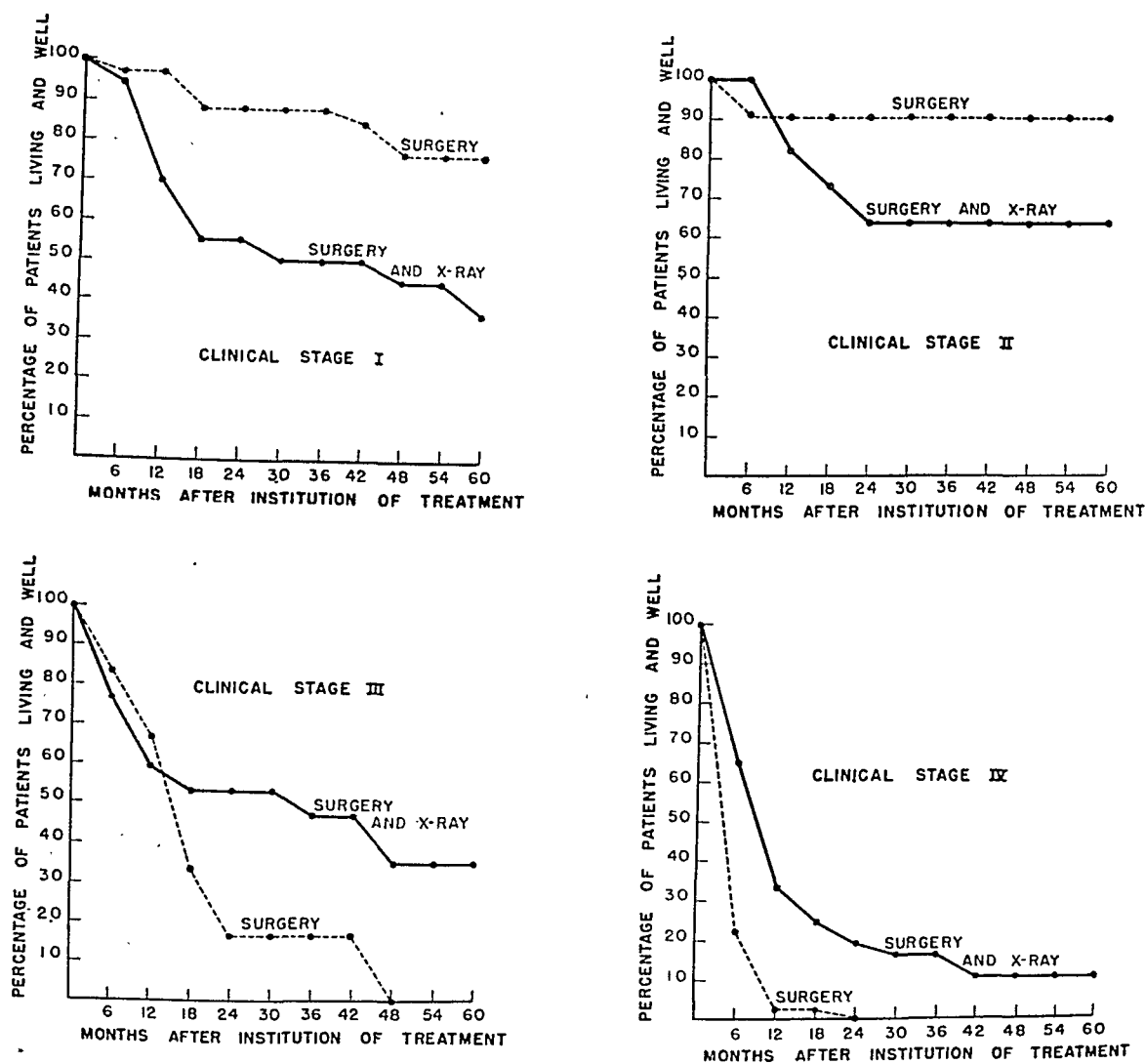


Fig. 6.—Survival curves—clinical extent of disease and method of treatment.

## VII. Recurrence and Death After Five Years

Five-year survival in postoperative ovarian cancer does not mean permanent cure. There were eight patients with recurrence or death after five years. Six of the eight were patients with papillary serous cystadenocarcinomas of border-

neoplasia, benign or malignant. It would seem that the occasional discovery of symptomless ovarian tumors would justify periodic pelvic examination of all women 35 or more years of age.

Dr. Taylor states that "surgery remains the keystone of the treatment of carcinoma of the ovary." With this statement we must agree wholeheartedly. There would seem to be little question of how much tissue to remove in patients with lesions apparently confined to one or both ovaries. Nevertheless, only one in four of 185 patients with ovarian carcinoma recently reported from the Royal Victoria Maternity Hospital and the Department of Obstetrics and Gynecology of McGill University had bilateral salpingo-oophorectomy and total or subtotal hysterectomy. Recently Diddle traced 294 women with ovarian carcinoma treated in the City of Dallas during an eleven-year period ending Dec. 31, 1946. Only one in nine of them had adequate operation, if subtotal hysterectomy can be classed adequate. Otherwise, only seven women, or one in forty-two, received acceptable treatment.

Several important observations arose from Diddle's work: Ninety patients of this series were submitted to bilateral oophorectomy and more than one-half had histologically proved carcinoma in both ovaries. One-third of forty-six women submitted to hysterectomy had extension of the malignancy to the uterine wall or to the endometrium. One-seventh of 122 women with one or both Fallopian tubes removed had tubal metastasis.

It would seem, therefore, that the other ovary, the Fallopian tubes, and the uterus are involved with sufficient frequency to necessitate removal. Moreover in this day and age when total hysterectomy can be done with negligible mortality rates, it would seem that there could be no valid reason for allowing the cervix to remain during the course of any operation aiming at eradication of ovarian malignancy.

To sum this up, I believe that in general total hysterectomy and bilateral salpingo-oophorectomy should constitute the minimum acceptable surgical procedure for operable ovarian cancer.

The question of whether or not to administer postoperative irradiation has perplexed us all. Abdominal radiation carries an appreciable morbidity in terms of nausea, severe and prolonged anorexia, enteritis, and colitis. Occasionally death results from obstruction and fistula. For these reasons it is particularly gratifying to have Drs. Taylor and Munnell break down their figures in an attempt to clarify the problem and suggest that in some instances postoperative x-radiation is unnecessary.

DR. GEORGE KAMPERMAN, Detroit, Mich.—I would like to show one table which presents the all-over results at Harper Hospital since 1923.

HARPER HOSPITAL  
FIVE-YEAR SURVIVALS OF CARCINOMA OF OVARY

DEEP ROENTGEN THERAPY					DEEP ROENTGEN THERAPY					SUPER VOLTAGE ROENTGEN THERAPY				
A	YEARS	CASES	WELL	PER CENT	C	YEARS	CASES	WELL	PER CENT	D	YEARS	CASES	WELL	PER CENT
	1923	4	-	-		1933	15	2	13		1933	11	2	18
	1924	11	3	27		1934	10	1	10		1934	7	2	28
	1925	9	2	22		1935	9	1	11		1935	7	-	-
	1926	7	-	-		1936	1	1	100		1936	11	2	18
	1927	10	2	20		1937	1	1	100		1937	16	6	38
	Total	41	7	17		Total	36	6	17		Total	52	12	23
B	1928	14	3	21							1938	25	6	24
	1929	13	1	8							1939	13	6	46
	1930	11	4	36							1940	12	4	33
	1931	12	1	8										
	1932	12	3	15										
	Total	62	12	17							Total	50	16	32

most papillary pseudomucinous cystadenocarcinomas; and most granulosa cell tumors. The best chances for survival occur in these cases.

6. Complete surgical removal of the internal genitals remains the treatment of choice in ovarian carcinoma. Conservative surgery is rarely justifiable.

7. Radiation therapy has a definite place in the treatment of certain cases of ovarian carcinoma chiefly to prolong survival time and perhaps occasionally (although rarely) to cure residual disease. It should be administered to all patients with tumors of high-grade histological malignancy even if localized to one or both ovaries. It seems of no value in tumors of low-grade histological malignancy unless there is operative evidence of spread beyond the ovaries; in the latter event, x-ray should be given. It should be given to all patients with extension of tumor beyond the ovaries regardless of the amount of spread and regardless of histological type.

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### Discussion

DR. WILLIAM MENGERT, Dallas, Texas.—Carcinoma of the ovary numerically ranks third among female genital carcinomas. Those of us with ward services see it infrequently and the average gynecological surgeon does not often encounter it. Consequently, Dr. Taylor and his associate, Dr. Munnell, are to be congratulated for presenting the results of such a large series. The work was thorough and the conclusions from the facts presented seem eminently sound.

Carcinoma of the ovary is a "silent" lesion, since the tumor has reached a considerable stage of development by the time it manifests itself to the patient. Moreover, there is an appreciable group arising in previously existing cystadenomas, although many primary ovarian cancers develop as such. Between one-eighth and one-fourth of all true neoplasms of the ovary are malignant. Therefore, it behooves us to beware of ovarian



Our incomplete statistical survey of this series does not yet permit comment upon the other problems introduced by Dr. Taylor. The similarity of our findings and final results does, however, emphasize that we are still far from attaining a satisfactory diagnostic and therapeutic attack upon ovarian cancer. Early diagnosis, which has been so effective in making possible the early treatment of external cancers, will likely be impossible in ovarian tumors until some blood or urine test is developed to show that the individual has a malignancy and thus to stimulate thorough search for its site. Let us hope that the investigations along this line now being so vigorously conducted will prove fruitful and thus provide us with a means of earlier diagnosis of all internal malignancies.

DR. EMIL NOVAK, Baltimore, Md.—The method of study employed by Dr. Taylor is an excellent one, and deserves emulation by others who will attack this problem in the future. There are, however, one or two points on which some issue may be taken. I do not know whether the authors are justified in making such a sharp differentiation between tumor type and cell differentiation factors, because they so commonly parallel each other. For example, a highly undifferentiated tumor is likely to be one in which the pattern is likely to be blotted out, so that, to give one illustration, it may be difficult to distinguish between a highly undifferentiated papillary cystadenocarcinoma and one of solid, medullary type.

More important, however, is the questionable justifiability of including in the classification of carcinomas certain cases which, from the slides which were shown, are clearly benign from a histological standpoint. It is beside the point to urge that in some cases of this type peritoneal implantation may occur, with the ultimate death of the patient. The same statement can be made of certain histologically benign pseudomucinous cystadenomas, which can bring about a histologically benign pseudomyxoma peritonei, with also ultimate death. Or it may be made of certain benign but locally invasive hydatidiform moles which may penetrate the uterine wall and occasionally cause fatal intra-abdominal hemorrhage. In other words, patients may die of histologically benign as well as histologically malignant ovarian tumors.

Since Dr. Taylor's otherwise excellent classification is a pathological and not a clinical one, it would seem that injection of the clinical consideration with one of his groups is like a mixing of metaphors. This is said with full appreciation of the fact that the papillary cystadenomas are as a group to be reviewed with more misgiving than the pseudomucinous, and that in an inevitable fraction of borderline cases pathologists will differ as to whether or not they are malignant. The first of the slides shown by Dr. Taylor, however, appeared to me not of this type, but definitely benign from a histological standpoint.

Finally, I would like to call attention to the fact that the sixteen cases of granulosa cell carcinoma in this series showed a survival rate of only 55 per cent, emphasizing a feeling I have long held that this tumor type is by no means to be taken as lightly as it is by some pathologists. This figure of 55 per cent would seem to me to be closer to the true one than the larger figure of 81 per cent survivals reported by Dr. Plass.

DR. LAWRENCE WHARTON, Baltimore, Md.—I should like to ask Dr. Taylor a question. Some time ago, I read a report of the very successful preoperative irradiation of inoperable ovarian carcinoma. This physician, however, reported three cases of large ovarian cancer which he operated upon but found inoperable. He did nothing but open and close the abdomen. In each instance, he followed the exploration by full roentgen therapy. The masses became much smaller, movable, and harder. The general condition of the patients improved. Eventually, he was able to remove these masses successfully. At the time of the report, these three patients had been well for eight to thirteen years since the operation.

I would like to ask Dr. Taylor whether he has had any such favorable experiences with irradiation in any of his cases of carcinoma of the ovary. I have had no such good results in my own experience, and the reports in the literature are not encouraging.

DR. WILLIAM P. HEALY, New York, N. Y.—I think it may be worth while to emphasize the value of postoperative irradiation in these cases of incompletely removed ovarian malignant tumors. There is a large series of ovarian tumors in which we did not consider

It will be noted that the cases are grouped in groups of five years each. Groups A, B, and C show results for each five-year period as obtained by ordinary deep roentgen therapy (200,000 watts). It is significant that for each five-year period the total five-year survivals remained at 17 per cent.

Groups C and D were run parallel, during identical years. Group C was treated with ordinary deep roentgen therapy (200,000 watts), while those in Group D were treated with supervoltage roentgen therapy (600,000 watts). The five-year survivals went from 17 to 23 per cent when supervoltage roentgen therapy was used. Three additional years of supervoltage roentgen therapy are added and the five-year survivals for the entire group for supervoltage roentgen therapy is 32 per cent as compared with 17 per cent for the ordinary 200,000 volt deep therapy. We believe this is too significant to be ascribed to mere coincidence.

We believe that roentgen treatment cannot be too rashly pushed aside as a treatment for carcinoma of the ovary. As evidence of this we like to cite three cases which showed multiple general carcinomatoses, and were considered inoperable so far as a cure was concerned. Yet after roentgen treatment, one survived fourteen years without evidence of extension and finally died of a cerebral accident. Two other similar cases with general metastasis in the omentum, peritoneum, and in the intestines, are alive and apparently well six years and four years, respectively, after the operation and treatment, and today no evidence of disease can be demonstrated by physical examination. We believe that roentgen therapy has a definite place in the treatment of carcinoma of the ovary and we feel every patient should have the benefit of this.

In general, the treatment at Harper Hospital consists in the surgical removal of the primary lesion and the larger masses, with subsequent deep roentgen therapy. We believe surgical treatment is necessary and part of making the diagnosis. As a prophylactic measure we like to follow the suggestions of Crossen to remove both ovaries when operating on patients 44 years of age or over.

DR. E. D. PLASS, Iowa City, Ia.—Since we have recently made a preliminary study of our cases of ovarian carcinoma seen between Jan. 1, 1926, and Dec. 31, 1943, it seemed that the results might be of some interest. There were 267 patients with proved primary ovarian malignancies. The five-year control rate was 28 per cent with the greatest loss in the first and second years after therapy. Survivals beyond that period obviously become increasingly complicated by the attrition of age, the influence of which we have so far been unable to evaluate. When the average age at appearance of a malignant tumor is 55 years, it is to be expected that the ravages of the degenerative diseases of the aging will take a toll and thus complicate evaluation of any treatment of the malignancy.

The survival rate has also been studied in regard to the histologic type of the tumor. The high percentage of salvage in the group of cystadenocarcinoma brings into focus the difficulty of accurate histological evaluation which Dr. Taylor stressed. Does not this merely mean that attempts to determine functional cellular alterations, in this instance invasiveness, are likely to be inaccurate when reliance is placed upon examination of fixed and stained tissues? Experience in correlating these histological changes with the clinical course of the patient has been the basis of our attempts at evaluation, but it seems obvious that in borderline situations it is none too good.

The results have been studied of the various available therapeutic procedures used. Surgery with removal of as much as possible of the original growth together with extirpation of the remaining adnexa and the entire uterus has proved the most effective. Supplementary x-radiation, whether given before or after operation, added practically nothing to the control rate. Our efforts to provide radiation before surgical attack were discontinued after a few humiliating errors proved that we were unable to diagnose ovarian cancer clinically. Since then x-ray therapy has been concentrated in the early postoperative period. Our results certainly raise the question of whether such additional treatment is worth while. Those patients offered no treatment had such far-advanced lesions that exploratory laparotomy only was advisable with removal of tissue for histological study, and the Department of Radiology declined to treat these women.

# QUANTITATIVE STUDIES ON THE PRODUCTION, DESTRUCTION, AND ELIMINATION OF CHORIONIC GONADOTROPIN IN NORMAL PREGNANCY\*

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THE study of endocrine patterns during normal and abnormal gestation is of both fundamental and practical importance. The present paper is concerned with a quantitative study of some aspects of the production and excretion of chorionic gonadotropin in normal pregnancy, and represents a summary of the work that has been carried out in our laboratory during the past two years.

Very early investigations<sup>1-5</sup> have shown that an active substance, now known as chorionic gonadotropin, is present in extracts of placenta, hydatidiform mole, and chorioepithelioma, and in the blood and urine of pregnant women. As is well known, it is the presence of this hormone in the body fluids of pregnant women that constitutes the basis for most biologic tests for pregnancy.<sup>6-14</sup> The origin of chorionic gonadotropin was at first erroneously ascribed to the anterior lobe of the pituitary gland, but later work,<sup>15-22</sup> especially the tissue culture techniques of Gey, Jones, Seegar, and Hellman, and others<sup>23-25</sup> established the trophoblast as being the source of this hormone. Its function in the human being has long been a matter of conjecture. Brown and Bradbury<sup>26-28</sup> have demonstrated that chorionic gonadotropin acts as a luteotrophic agent for the newly formed corpus luteum, but whether or not chorionic gonadotropin has any other function, particularly in the last two trimesters of gestation, is unknown. The concentration of hormone in the blood and its urinary excretion in normal pregnancy have been studied quite extensively.<sup>29-32</sup> A rather characteristic pattern is present, consisting of a rise in both serum concentration and urinary excretion between the fiftieth and seventieth days of pregnancy, and a fall to a lower, constant level for the remainder of pregnancy. The hormone disappears from both blood and urine within a few days after delivery.

Despite these investigations, there is still a dearth of information concerning the normal values of serum chorionic gonadotropin. This unfortunate situation is due to the fact that many workers have used assay methods which have only local significance, since no two assay methods can be expected to yield identical results. The data of Delfs and Jones,<sup>33</sup> Rubin, Dorfman, and Miller,<sup>34</sup> and Gastineau, Albert, and Randall<sup>35</sup> are exceptional in that they are presented in terms of International Units, but they comprise less than fifty cases in all. Because of the recent importance<sup>36-42</sup> attached to abnormal hormonal values in toxemia of pregnancy, it seemed worth while to obtain a sufficient series of normal values in terms of International Units, so that results of different labora-

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postoperative irradiation to be of value, such as in an encapsulated tumor mass in the borderline groups or in the adenoma malignum type of tumor in which you do total hysterectomy and bilateral salpingo-oophorectomy where there is nothing to suggest residual tumor growth. What would you irradiate there? Postoperative irradiation is not indicated in a case of that type, even if you do have a low-grade malignant tumor unless and until there is palpable tumor tissue present on subsequent follow-up examination. On the other hand, in other cases of malignant ovarian tumors where you are definitely unable to remove all the tumor tissue beyond any question of doubt, as indicated by Dr. Wharton's question, we have had in a limited number of cases very satisfactory response to postoperative irradiation in the way of prolonged life, not necessarily a five-year cure but prolongation. In the dysgerminoma group you are astounded at times at their remarkable response to roentgen irradiation in the way of total disappearance of extensive tumor masses. Those patients will live five or more years, so I think it would be very wrong to leave any impression that postoperative irradiation should not be utilized in an incompletely removed ovarian tumor.

DR. TAYLOR (Closing).—This discussion has emphasized the fact that if the results in carcinoma of the ovary are to be correlated with the various techniques of treatment, we cannot publish reports on total cures. Ovarian carcinoma is a group of diseases and not a single one. Although it is tempting to report the absolute cure rate for all cases of ovarian cancer, such a report is much less meaningful than five or six smaller reports on each of the divisions, each such study being based on a homogenous group of tumors.

Dr. Wharton asked about the apparent improvement after incomplete removal of ovarian carcinoma. While at Roosevelt Hospital I reported four cases in which operation was done and some but not all of the tumor was removed. Each case was either followed for ten to fifteen years or else reoperated upon for some other purpose. Spontaneous regression of the tumor was thus demonstrated. These four cases were, with regard to histology, of this borderline type.

I would like to defend two points which Dr. Novak attacked. First, he said that it was impossible to classify all types because when they became sufficiently undifferentiated no one can tell the type of cell they were derived from. That is absolutely true and in our tables there was one category for totally undifferentiated tumors. These tumors are, we believe, usually a form of extremely undifferentiated serous cystadenoma carcinoma, but the original characteristics of the cells are so lost that no one can say positively whether they were pseudomucinous or serous. You will always have a certain group of cases in which you cannot determine the histogenesis.

The other point is how to classify the case with borderline histology. Dr. Novak believes these are not histologically malignant and yet they may kill the patient. Here we may argue about the meaning of malignancy and whether structure or results define the word. I would prefer to study the life history of the tumor first and later decide from the life history what structure justifies the designation "malignant." There were nineteen cases in our borderline group among which the tumor recurred in two patients within five years and in three patients after longer intervals. This seems to me a fair demonstration of the biologically malignant quality of these tumors.

The major point, however, is to have some agreement on classification and I hope that we may soon develop a standardized system so that the results of different clinics may be compared with each other. We cannot do that if we continue to speak of total ovarian carcinomas and not of individual groups.

The shape of the curve as indicated by plotting the mean values indicates a peak level in concentration of hormone occurring about the fifty-fifth day after the last menses. A gradual reduction occurs, so that from the hundredth day until parturition a fairly steady level of about 20 I. U. per cubic centimeter of serum is present. These values are in good agreement with those reported by others.<sup>33</sup>

The establishment of a sufficient number of normal determinations makes it possible to study the role of chorionic gonadotropin in abnormal states, particularly the toxemias. This is of prime clinical importance, since there is some controversy as to the behavior of this hormone in toxemia. The Smiths<sup>36-42</sup> have pointed out that a rise in serum gonadotropin occurs four to six weeks prior to the appearance of toxemic symptoms, and White and her associates<sup>44-48</sup> have attached great significance to this finding in terms of therapy. However, Taylor and Scadron<sup>49</sup> have been unable to confirm this rise in serum gonadotropin. Rubin, Dorfman, and Miller<sup>34</sup> studied intensively five cases of diabetes associated with pregnancy. In two of three patients who had no signs of toxemia the serum gonadotropin levels were normal, and in the third patient the levels were significantly increased. Of two patients with clinical signs of toxemia, one patient with mild toxemia had normal levels of chorionic gonadotropin and the other, with severe toxemia, had significantly increased levels of gonadotropin. It appears then that there is some uncertainty concerning the significance of abnormally high levels of serum gonadotropin in toxemia. The establishment of our series of normal values will therefore be of great use in determining abnormal levels in toxemia, a study that is now in progress.

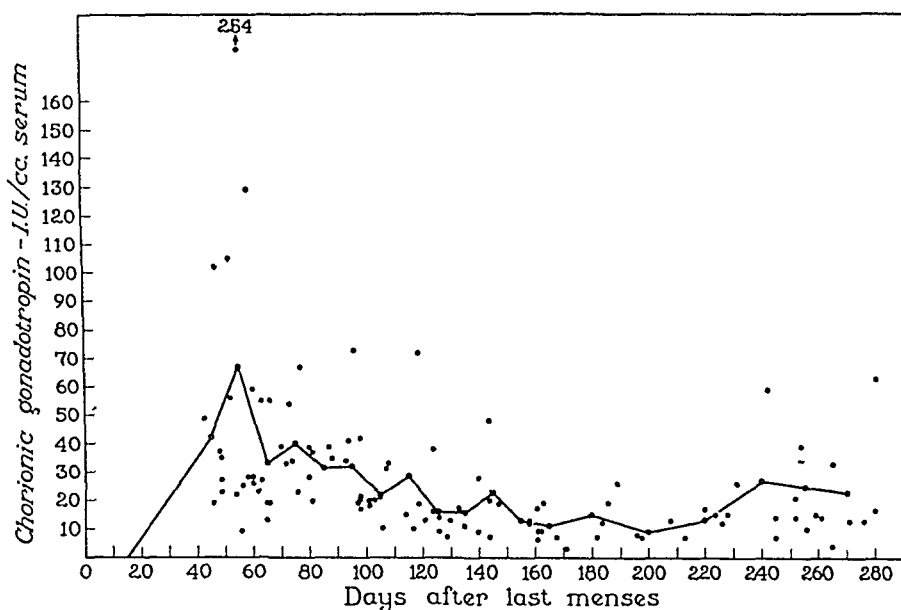


Fig. 1.—Concentration of serum chorionic gonadotropin in 112 subjects during normal pregnancy.

*B. Factors Influencing the Characteristic Pattern of Chorionic Gonadotropin in Blood and Urine.*—As was pointed out previously, the level of hormone in serum and urine may be the resultant of many factors. In the opinion of Browne, Henry, and Venning<sup>29, 30</sup> the peak excretion reflects a physiologic necessity in order that the function of the corpus luteum in early pregnancy may be maintained. Additional support to the concept of increased production has come from the histologic studies,<sup>21-25</sup> which indicate a direct proportionality

tories could be readily compared, and so that any single determination could be satisfactorily classified as normal or abnormal. The first phase of our work has therefore been directed toward the establishment of normal values in terms of an absolute and universal standard of measurement in a sizable population of normal pregnant women.

The second phase of our work has been directed toward an analysis of the factors which might determine the characteristic pattern of the fluctuations in chorionic gonadotropin during normal pregnancy. It is fairly obvious that the amount of hormone present in serum at any given time must represent the difference between the amount produced during that time, and the sum total of all metabolic processes that might inactivate the hormone, utilize it, and eliminate it from the body during that time. For example, does the peak in serum and urine which occurs between the fiftieth and seventieth days represent an increased production of the hormone, or a decrease in either renal elimination or destruction? Does the lower urinary elimination during the last two trimesters indicate an altered renal function with respect to this hormone? Again, the recent importance attached to the utilization theory of this hormone in abnormal states makes it highly desirable to learn what factors determine the normal patterns of excretion. Any concept of the role of this hormone in abnormal states of pregnancy could be considered as only tentative until as many factors as might influence the level of this hormone in normal pregnancy could be delineated. Consequently, we have attempted to resolve the relative importance of such factors as production and excretion (renal and extrarenal) on the normal fluctuations of this hormone.

### Material and Methods

Approximately 132 normal pregnant women furnished the basis for our studies. These were patients routinely seen and followed in the Section on Obstetrics and Gynecology of the Mayo Clinic. Venous blood and twenty-four-hour collections of urine were obtained from these patients at various intervals of pregnancy and during the immediate post-partum period. Chorionic gonadotropin was determined by the method of Albert.<sup>43</sup> Briefly, this method utilizes ovarian hyperemia as an end point, and consists in determining the median effective dose by serial dilution of either blood or urine. Since the median effective dose is 1 I.U., the amount of hormone in International Units per cubic centimeter can readily be calculated by the dilution factor, and in turn for the entire circulating serum or twenty-four-hour urine specimen. The chief advantage of this method is its speed and convenience, thus permitting work on an extended basis. Its over-all accuracy is  $\pm 30$  per cent.

### Results

*A. Level of Chorionic Gonadotropin During Normal Pregnancy.*—The results of single determinations in 112 normal pregnant subjects are shown in Fig. 1. No attempt was made to follow any of these patients serially, since this has already been studied by Delfs and Jones<sup>33</sup> and also by Gastineau, Albert, and Randall.<sup>35</sup> The use of single determinations in many patients seemed to us to have more clinical significance than serial determinations in a few patients, for it allows a better view of the extent of variation in entirely normal pregnant subjects.

Since the renal elimination of hormone cannot account for the hormonal pattern, the remaining two possibilities—changing production and changing utilization (or destruction, or extrarenal disposal)—were investigated. It is difficult to determine the rate of production directly by experimental or other means. However, an indirect estimation of this factor could be obtained if it were possible to determine how much hormone was disposed of by all processes other than renal elimination. Such processes would represent the total of endogenous destruction, utilization or excretion by routes other than the kidneys. Such an estimation is also difficult to obtain directly, since a direct experimental solution would involve the injection of chorionic gonadotropin during pregnancy and the measurement of its fate, distribution, and excretion. Since, in pregnancy, endogenous hormone is being produced, perhaps at a variable daily rate, the results of such determination would be fraught with some uncertainty. The use of nonpregnant patients in studies of this sort has therefore been resorted to by others, but it is to be recalled that the results of such investigations are not necessarily applicable to the pregnant subject.

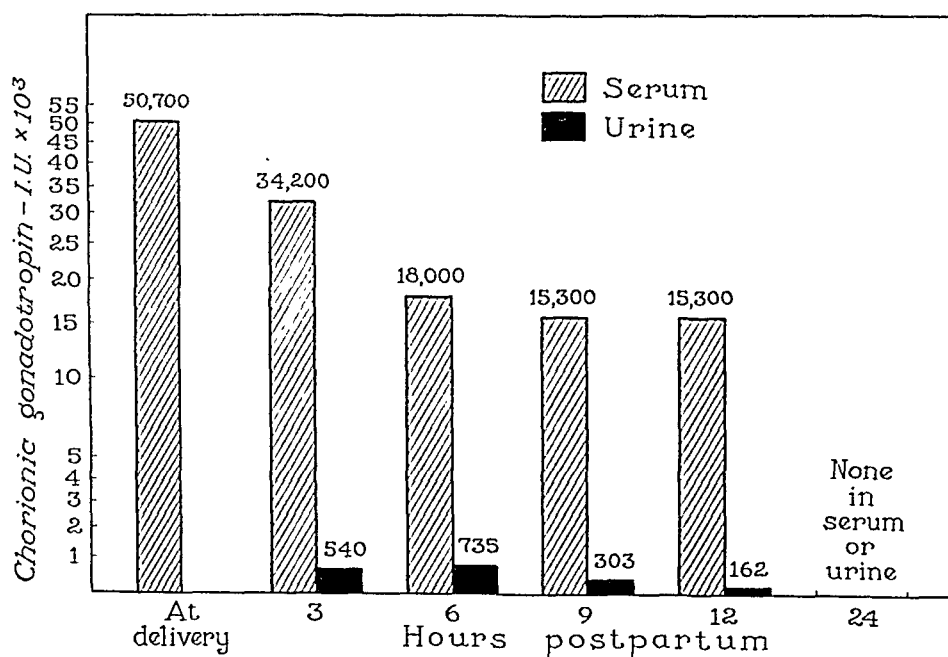


Fig. 3.—Total chorionic gonadotropin in serum and urine at various intervals after delivery.

As a compromise approach, the following attack was chosen by Johnson, Albert, and Wilson.<sup>50</sup> The concentration of hormone in serum was determined at the time of delivery in fifteen normal pregnant women, and also in all of the urine excreted after delivery. From these values, the total amount in the circulating blood serum can be estimated as the product of the concentration of hormone in serum and the total volume of serum, estimated at 5 per cent of body weight or approximately 3 liters. The total amount of the hormone appearing in the urine was determined directly. If all of the serum hormone appeared in the urine, then it would seem that none of it was disposed of elsewhere, or destroyed or utilized. The results of this study, an example of which is shown in Fig. 3, indicate that only 6 per cent of the hormone in the serum appears in

between the number of Langhans' cells and the amount of hormone eliminated. On the other hand, Smith and Smith<sup>42</sup> have emphasized that the production and utilization of hormone are regulated by the steroids produced during pregnancy.

However, the role of the kidneys has never been evaluated satisfactorily. Since it is possible that changes in renal function during pregnancy would lead to changes in the concentration of hormone in the serum, renal function with respect to chorionic gonadotropin was studied by Gastineau, Albert, and Randall.<sup>35</sup> Five normal patients were observed throughout pregnancy and the renal clearance of chorionic gonadotropin was determined. An example of this study is given in Fig. 2. The clearance of hormone (that is, the volume of blood cleared of chorionic gonadotropin per minute) was found to remain constant at a level of about 0.38 c.c. per minute throughout pregnancy, despite the fact that the concentration of hormone in the blood was much higher in the first trimester than in the last two trimesters. Thus, the characteristic hormonal pattern is not due to changes in renal function during normal pregnancy. The possibility still remains, however, that in abnormal pregnancy such as toxemia, the rise in serum levels could result from altered renal function. The study of renal clearance of hormone in these states would furnish such much-needed evidence.

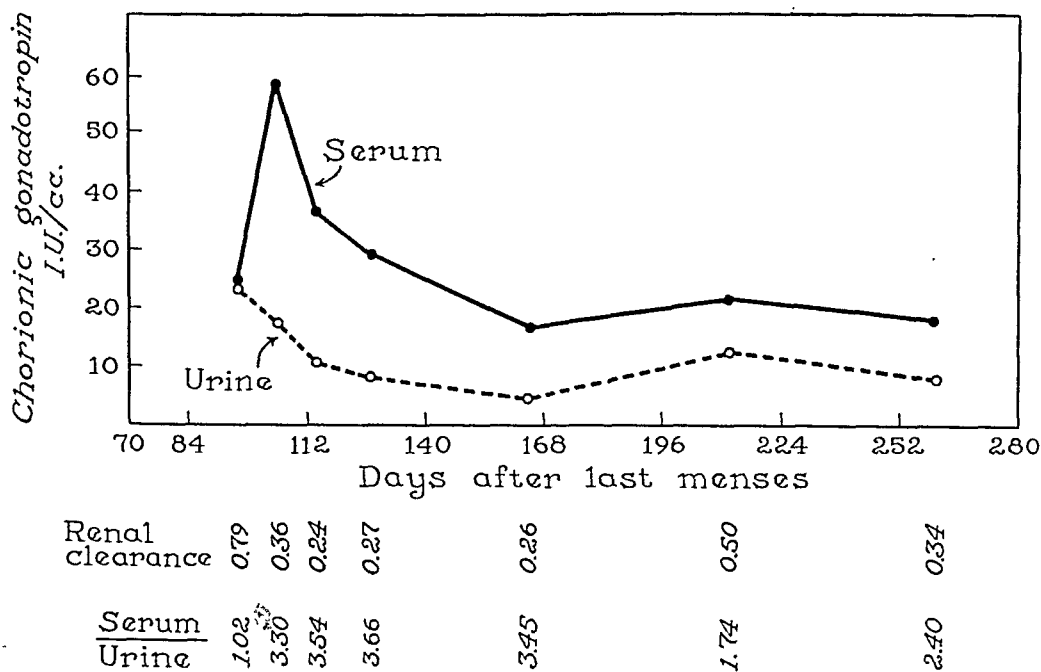


Fig. 2.—Simultaneous serial assays for chorionic gonadotropin in a normal pregnancy, with renal clearances and serum-urine ratios.

Clearance: The volume of plasma, in cubic centimeters, containing the same amount of substance as is found in one minute's urine.

Example 1. Clearance:

$$\frac{30,300 \text{ (I.U. chorionic gonadotropin in 24-hour urine)}}{1,440 \text{ (number of minutes in 24 hours)}} = 21 \text{ I.U. in 1 minute's urine}$$
$$\frac{21 \text{ (I.U. chorionic gonadotropin in 1 minute's urine)}}{58.7 \text{ (I.U. chorionic gonadotropin in 1 c.c. of serum)}} = 0.36 = \text{renal clearance}$$

Example 2. Ratio:

$$\frac{58.7 \text{ (I.U. chorionic gonadotropin in 1 c.c. of serum)}}{17.8 \text{ (I.U. chorionic gonadotropin in 1 c.c. of urine)}} = 3.30 = \text{serum-urine ratio}$$



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## Discussion

DR. WILLARD M. ALLEN, St. Louis, Mo.—There are several points in Dr. Randall's paper which are of unusual interest.

I wonder if the levels of chorionic gonadotropin which are supposedly uniformly high in early pregnancy are really as high as we suppose. In his studies there are numerous observations at about the fiftieth day after the last menstrual period which do not seem to be so very much greater than observations made at much later stages of pregnancy.

The rate of disappearance of the hormone after delivery of the placenta is very revealing. He finds that only 10 per cent of the amount of hormone estimated to be present in the serum at the time of delivery ever finds its way into the urine following delivery. This correlates very well with other studies on the excretion of sex steroids. Studies of that type usually show that approximately 10 per cent of the injected material appears in the urine. What happens to the other 90 per cent?

The liver is considered to be the organ responsible for the inactivation of the sex steroids. Is it also the organ responsible for the destruction of chorionic gonadotropin?

We will anxiously await his studies on renal clearance of chorionic gonadotropin in the toxemias now that the basic work on normal pregnancies has been done.

DR. GEORGE VAN S. SMITH, Brookline, Mass.—Dr. Randall's paper raises many questions. It was gratifying to see that the curve of chorionic gonadotropin he presented is almost exactly similar to the curve we were the first to publish in 1936, based on the simple Aschheim-Zondek method.

I would like to ask Dr. Randall if he can offer any explanation for the finding of high chorionic gonadotropin preliminary to the development of toxemia of pregnancy.

the urine. The remaining 94 per cent must therefore be destroyed, utilized, or disposed of by other means, since the production of the hormone has ceased, owing to the removal of the placenta.

The estimation of extrarenal disposal of circulating hormone to the extent of 94 per cent is in excellent agreement with the results obtained by Zondek and Sulman<sup>51</sup> in animals. They have found that only 5 to 10 per cent of injected hormone appears in the urine, and that a large portion of the remainder is destroyed by tissues of the body. However, our estimations are at variance with the work of Bradbury and Brown,<sup>52</sup> who stated that relatively little destruction or utilization of the hormone occurs in the human being (nonpregnant women). Whether this discrepancy is due to differences in method or interpretation, or to a difference in behavior of nonpregnant subjects as opposed to those just delivered remains to be determined.

At any rate, it seems reasonable to regard the characteristic hormonal pattern as resulting from changes in the rate of production, since the renal disposal remains constant throughout pregnancy, and since there is no valid reason to suppose that the extrarenal disposal varies during pregnancy. This view, which is supported for the first time by direct and indirect experimental data, is in agreement with the opinion expressed earlier by Browne and Venning,<sup>29</sup> and by Wislocki, Dempsey, and Fawcett<sup>22</sup> on the basis of histologic methods.

### Summary

The levels of chorionic serum gonadotropin in normal pregnancy have been determined in 112 patients in terms of International Units. A characteristic curve for this hormone has been obtained, agreeing in both pattern and absolute values with those reported by others. An analysis of the factors which might influence the characteristic hormonal pattern indicates that the renal function with respect to the hormone remains constant during normal pregnancy, that the extrarenal disposal of the hormone accounts for more than 90 per cent of the circulating hormone, and that probably the fluctuating character of hormonal level in serum or urine depends entirely on changes in rates of production of hormone during pregnancy.

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# A SERIES OF POTENTIALLY ABORTIVE OVA RECOVERED FROM FERTILE WOMEN PRIOR TO THE FIRST MISSED MENSTRUAL PERIOD\*

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## Introduction

IT IS the purpose of this paper to present some observations which may throw light on the etiology and pathogenesis of spontaneous abortion. Since the latter occurs in approximately 10 per cent of patients who are clinically pregnant and undoubtedly is present, but unrecognized, in some patients complaining of sterility, the relationship of this subject to infertility is obvious.

In the past there have been two schools of thought with regard to the etiology of spontaneous abortion. The late Dr. Mall<sup>1</sup> believed that an abnormal uterine environment was responsible for this ovular wastage. On the other hand, the late Dr. Streeter<sup>2</sup> and his group believe that there is something intrinsically wrong with the fertilized ovum itself—expressed by the general term of “germ plasm defect”—rather than with the maternal environment.

## Material

During the past ten years, from November, 1938, to October, 1948, Dr. Rock and I have been studying at the Free Hospital for Women various aspects of human reproductive physiology and pathology. Within this period of time we have discovered twenty-eight early human conceptuses in uteri removed therapeutically for a variety of reasons. None of the patients had missed their next expected menstrual period so that these specimens are younger than sixteen days of age.

The 136 cases,† which comprise the study group from which these specimens were obtained, are a special group of fertile patients in whom pregnancies might occur. Indeed they had averaged nearly five normal pregnancies per patient. A preliminary report on the smaller series then extant was made in 1942 before

\*Paper presented by Dr. Hertig. This study has been aided by grants from the Carnegie Corporation of New York and the William F. Milton Fund of Harvard University. It has been read, in part, before the Conference on Menstruation and Its Disorders, January, 1947, New York City. Permission to reprint parts of the text and illustrations has been generously granted by Charles C Thomas, Publisher, publisher of the proceedings of that conference.

†Since October, 1948, eleven additional uteri have been searched for early conceptuses, three of which have been found. They are not included in this series since none have been completely studied although two free-lying segmenting forms are briefly mentioned in the text to illustrate a normal 4½-day blastula (Fig. 1) and an abnormal five-cell morula (Fig. 3).

DR. OLIVE SMITH, Brookline, Mass. (by invitation).—One important point in the curve Dr. Randall presented was that it confirmed our finding of a tendency for chorionic gonadotropin to rise at the termination of normal pregnancy. I wonder if there is any evidence for increased production at the end of pregnancy?

DR. GEORGIANNA JONES, Baltimore, Md. (by invitation).—I would like to say a few words about the chorionic gonadotropic assays which we have done. We have reported twenty-five normal patients with assays weekly throughout pregnancy. In addition, we have studied approximately fifty patients with abnormal reproductive histories who have gone through pregnancy normally and twenty-five or thirty patients who have aborted. As Dr. Smith has said, it is gratifying to know that the curves done in almost all the laboratories throughout the country are fairly similar. I think there is very little doubt that the rise in chorionic gonadotropic titer at about the sixtieth day does occur in normal pregnancy consistently. We have never studied a normal pregnancy or a pregnancy that went to term in which the titer has not risen to at least 40,000 I.U. per liter from a level of 2,000 to 3,000. It is certainly true also that around the 210th day in normal pregnancy there is a secondary elevation. In our cases, instead of rising from 40,000 to 100,000 I.U. as it does at the fiftieth to sixtieth day of pregnancy, the titer seldom goes above 20,000 and I believe our highest normal case was 30,000 I.U. per liter. In our experiences these values usually drop before delivery. It would be desirable to have an explanation of this rise, but I would like to point out that such a rise late in normal pregnancy makes the interpretation of a rise in abnormal pregnancy very difficult.

DR. RANDALL (Closing).—It is evident by this brief paper and its discussion that what we have presented here today represents an exploration into a complicated field.

Dr. Smith asks a very pertinent question. I would like to be able to answer it: whether this renal clearance would answer the question of why high levels occur, I do not know. In exploring this field, and we feel it is very important, we have to date stayed away from abnormal pregnancies. It has been pointed out that until we had sufficient experience in the normal pregnancy we had no right to explore the abnormal field. We believe now we have advanced to the state where we can examine excretion of the hormones in abnormal pregnancies and I hope to be able to report on this later.

In this matter of the end of pregnancy rise we have felt perhaps it was not sufficient to be significant. I do not know that that is a very safe statement to make but as we have plotted them in the last part of pregnancy we have felt there is no significant rise, but now I believe there is and its significance makes one pause a bit. If there is a rise in both abnormal and normal pregnancy I will be unhappy because I think it would be easier to explain a perfectly flat curve.

known fertile women who have recorded coital data during the probable ovulation time of any one menstrual cycle.

Of the twenty-eight early pregnancies obtained, twelve were interpreted by Drs. Streeter, Corner, and ourselves as being abnormal in one way or another. Ten of these specimens will be described and illustrated in some detail within the text. For comparative purposes, a normal blastula as well as a previllous and early villous ovum will also be described so that you may see wherein the abnormal differs from the normal.

It is my pleasure, as always, to acknowledge the help and cooperation of Drs. George L. Streeter,\* George W. Corner, and Chester H. Heuser, Messrs. Chester Reather, James F. Didusch, and O. O. Heard, Mrs. Miriam Menkin, and the Misses Susan Hedge and Eleanor Adams, without whose various skills this material would not be available for study.

### I. Normal Ova

Although not included in the present series because of incomplete study, Fig. 1 illustrates the youngest normal human ovum thus far observed. The blastula was found free in the uterine cavity on the nineteenth day of the menstrual cycle. Its maximum diameter is approximately  $130\ \mu$  and it is composed of approximately sixty cells. The larger and eccentrically located ones represent the embryonic mass whereas the smaller peripheral lying ones are to form the future trophoblast. The general form of the specimen is seen in Fig. 1,A while the microscopic details of the mid-sagittal section are seen in Fig. 1,B.

In Fig. 2 are two normal specimens represented merely for comparative purposes. The 12-day ovum, previously published in 1941,<sup>4</sup> is represented by a mid-cross section seen in Fig. 2,A. Its essential features are clearly evident and are briefly described as follows: The ovum is well implanted although not as yet completely covered by the endometrium. The normal late secretory endometrium, comprising the implantation site, shows a moderate predecidual reaction of the stroma about the ovum. The serrated, secretorily active glands contain inspissated glycogen-containing mucus. The trophoblast, or outer shell of the ovum, is composed of the more peripheral syncytiotrophoblast and the inner cytotrophoblast. The former contains intercommunicating lacunae within which is maternal blood, whereas the latter are proliferating in masses to form the future chorionic (placental) villi. The chorionic cavity is the most conspicuous feature of the normal ovum at this stage and is the lineal descendant of the segmentation cavity of the blastula as seen in Fig. 1. (It may be absent as will be noted (Fig. 5) in one of the pathological specimens.) The cavity is lined by an imperfect membrane originally described in the monkey by Heuser in 1932.<sup>5</sup> It is continuous with the primitive entoderm of the germ or embryonic disc. The latter also possesses primitive ectoderm and is thus double layered. A primitive amnion, attached to the edge of the ectoderm, is also present at this stage.

\*Deceased, July, 1948.

this Society by Rock and Hertig.<sup>3</sup> The finding of twenty-eight early pregnancies in the present series of 136 potentially pregnant patients thus gives us a fertility index of 20.6 per cent. To be sure, these patients are naturally past their reproductive prime since as a group they are older and, moreover, have come to a gynecological clinic for a variety of complaints. Nevertheless, to our knowledge, this is the only recorded index of human fertility in a group of

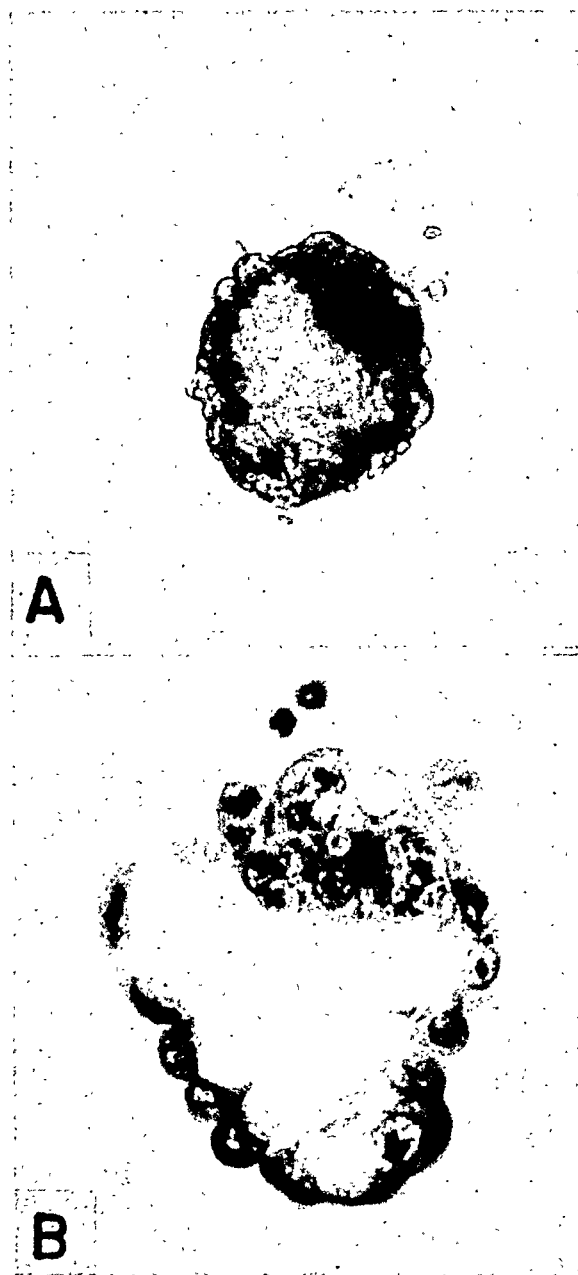


Fig. 1.—A normal human blastula of approximately  $4\frac{1}{2}$  days of age recovered from the uterine cavity on the nineteenth day of the menstrual cycle. Carnegie No. 8663.

A, Intact blastula after fixation and partial dehydration. The segmentation cavity and variation in thickness of the wall is readily made out. Sequence 3  $\times$  300.

B, A cross section of the blastula taken to include a significant diameter of the embryonic mass. The latter, composed of larger cells, is in the upper portion of the picture. The smaller cells composing the wall of the blastula are destined to become trophoblast and hence form the chorion. The prominent segmentation cavity, in the center of the blastula, is thus destined to form the chorionic cavity. Note two maternal cells, one a polymorphonuclear leucocyte, above the embryo which give some idea of the relative size of the blastula and its component cells. Section 6  $\times$  600.

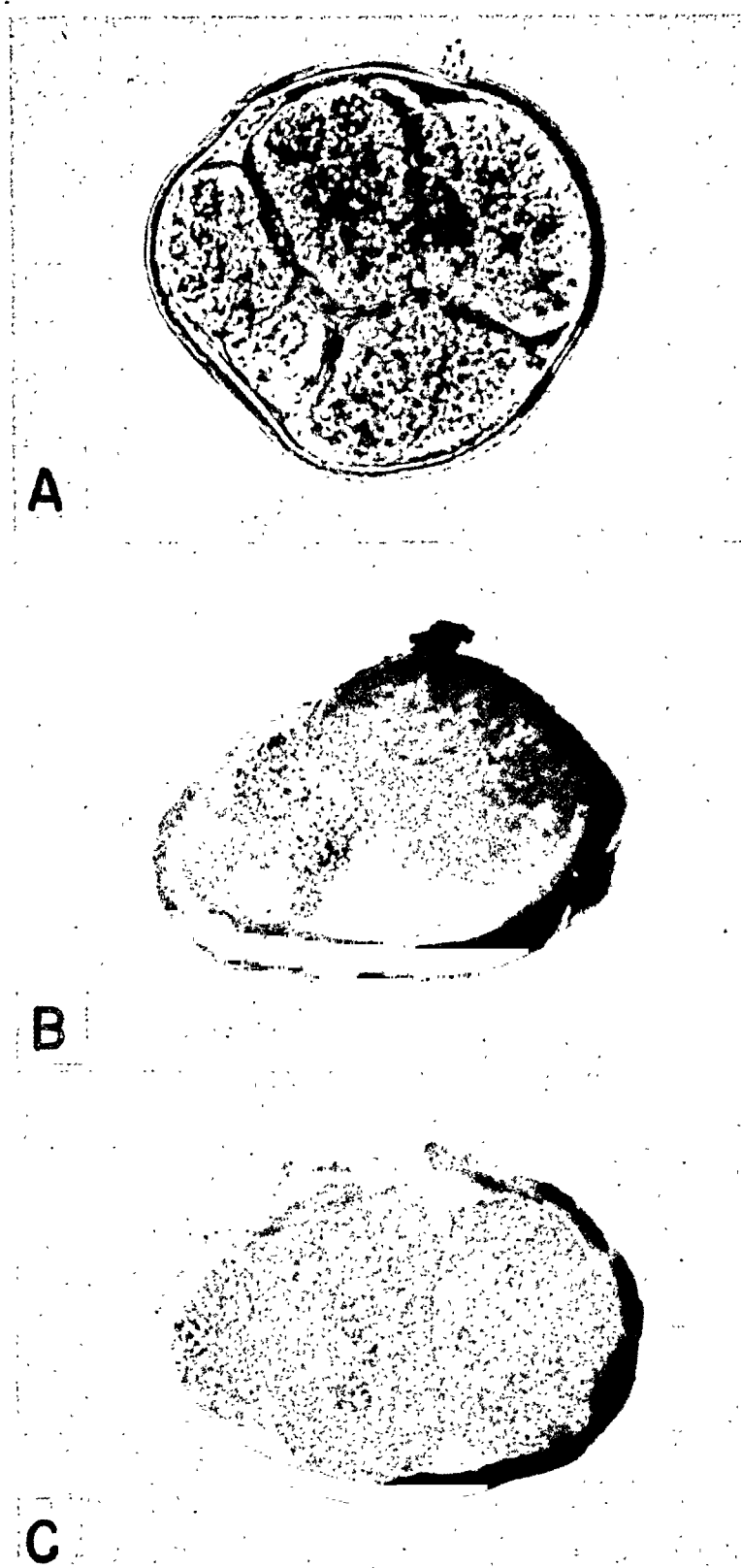


Fig. 3.—A five-cell abnormal human morula of approximately 4½ days of age. (Compare with Fig. 1, a normal specimen of comparable age.) Carnegie No. 8630.

A, Intact specimen after fixation and partial dehydration. Note variation in size of blastomeres most of which contain two or more nuclei. Sequence 7 × 500.

B, A parasagittal section to show variation in size of blastomeres, poor staining quality of cytoplasm, and multiplicity of nuclei. Section 6 × 600.

C, A mid-sagittal section to show portions of three blastomeres whose cell boundaries are indistinct, their cytoplasm muddy and nuclei multiple. Section 10 × 600.

The 16-day stage, represented by a normal early villous specimen, is seen in mid-cross section in Fig. 2,B. Its histological details are less evident than in the younger specimen because its much larger size makes a smaller magnification necessary. However, the interstitial type of implantation is now evident since the ovum is fairly well covered by regenerating endometrium. The early compact decidual reaction of the endometrial stroma about the ovum is easily seen. The most conspicuous feature of the ovum itself is the presence of early branched



Fig. 2.—A, A normal 12-day human ovum shown in mid-cross section. Carnegie No. 7700, section 5-7-7  $\times 100$ .

B, A normal 16-day human ovum shown in mid-cross section. Carnegie No. 7802, section 44-3-5  $\times 30$ .



chorionic villi. The large chorionic cavity, lined with primitive connective tissue, contains an embryonic disc which now has a double layered yolk-sac and a definitive amnion.

## II. Abnormal Ova

### 1. *Segmenting, Free in the Uterine Cavity.*—

Although not included in the present series because of incomplete study, Fig. 3 illustrates the youngest abnormal human ovum thus far observed. It was found free in the uterine cavity on the nineteenth day of the menstrual cycle and is, therefore, about  $4\frac{1}{2}$  days of age. It is composed of five blastomeres and its maximum diameter is approximately  $200\ \mu$ . It is abnormal on at least two counts: (1) its relatively immature embryonic development when compared to the normal  $4\frac{1}{2}$ -day blastula (Fig. 1) and (2) the large number of nuclei in the individual blastomeres. This multiplicity of nuclei in the cells of the segmenting ovum has characterized all the other abnormal free forms found in this study (Fig. 4).

The youngest completely studied specimen in the present abnormal series is a nine-cell segmenting ovum (Fig. 4,C) recovered as a free morula from the uterine cavity approximately three to four days after ovulation and subsequent fertilization. The associated active recent corpus luteum with unhealed stigma, the Fallopian tube, and endometrium were all normal. The latter was in the late seventeenth or early eighteenth day of the cycle. The glands were markedly tortuous and beginning to secrete glycogen-containing mucus. This was apparent as a wide, fairly regular zone of vacuolization in the basal portion of the glandular epithelium. This specimen together with its endometrium was published in 1946<sup>6</sup> in the Proceedings of the Conference of Diagnosis in Sterility. Details of its structure were also presented before The American Association of Anatomists in 1946.<sup>7</sup> Its oval and presumably abnormal shape is evident in Fig. 4,C, representing one of fifteen perfect serial sections cut by Dr. Heuser. Of the nine blastomeres in the specimen, only five contain a single nucleus, three contain two nuclei, while the remaining one possesses three. It is the presence of these multinucleated cells, together with its oval shape, which makes this specimen appear to be abnormal.

Two other segmenting human ova are available for comparison in Fig. 4, although they have not been reconstructed as yet. One of them, Figs. 4,A and B, has only eight blastomeres and is therefore slightly younger than the previous specimen. Two of the blastomeres are beginning to undergo necrosis (Fig. 4,B) whereas at least one of the viable cells possesses two nuclei (Fig. 4,A). Furthermore, it is flattened in one plane although circular in the other. Thus it is probably abnormal though it confirms the fact that the eight- to nine-cell human ovum is present as a free morula in the uterine cavity by the eighteenth day of the menstrual cycle. The endometrium, as in the nine-cell specimen, was perfectly normal.

The third segmenting specimen, also probably abnormal although somewhat more normal than the two others, has approximately twelve blastomeres (Fig.

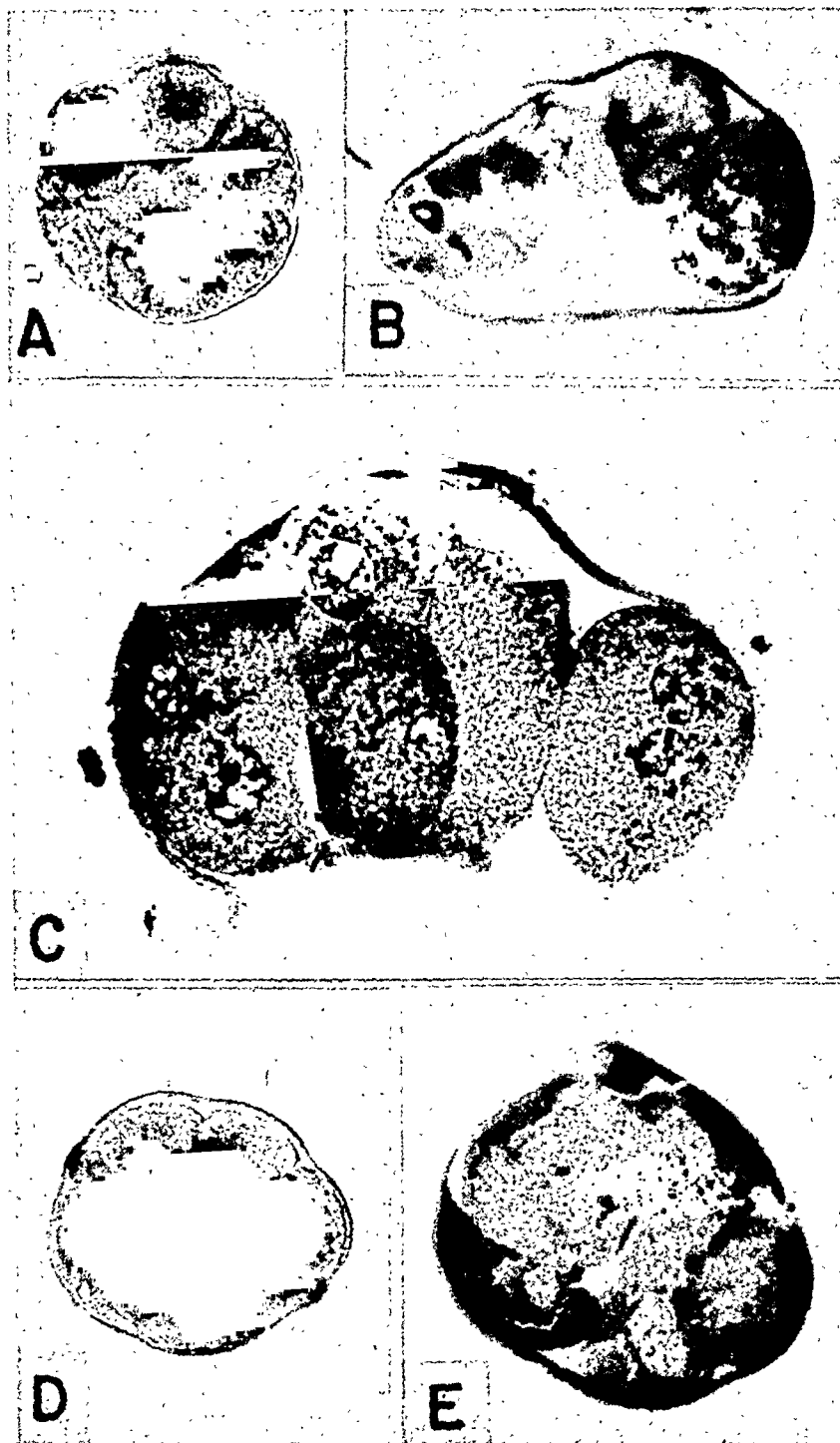


Fig. 4.—Three abnormal human morulas of approximately  $3\frac{1}{2}$  to 4 days of age recovered from the uterine cavity. A and B show an eight-cell specimen, Carnegie No. 8450. C shows a nine-cell specimen, Carnegie No. 8190. D and E show a twelve-cell specimen, Carnegie No. 8452.

A, Intact specimen shown by transmitted light. Sequence 7  $\times$  300.

B, Mid-cross section to show the flattening of the morula and the degenerative nuclear changes in two of the four blastomeres. Section 8  $\times$  500.

C, A section through the greatest diameter of the specimen to show the oval outline of the morula and six of its blastomeres, some of which are multinucleated. Section 8  $\times$  600.

D, Intact specimen viewed by transmitted light. Sequence 2  $\times$  300.

E, One of serial sections through the greatest diameter of the specimen to show the variable size, shape, and staining reaction of the various blastomeres. Note double nucleus toward 6 o'clock. The nuclei in general are not distinctly outlined nor are the individual blastomeres clearly demarcated. Section 8  $\times$  500.

thelium-like trophoblast at the embryonic pole to an indifferent stage at the equator of the ovum where the latter has contact with maternal tissue. (Thus, this part of the 7½-day ovum may be quite comparable to the embryonic pole of an implanting blastocyst soon after attachment to the endometrium.)

Since syncytiotrophoblast is apparently only slightly less primitive than the indifferent variety, it may be postulated that this very abnormal ovum possessed only this relatively limited ability to differentiate. The lack of cytotrophoblast or embryo, and more particularly a chorionic cavity, would tend to indicate that the preimplantation form of this ovum consisted of merely a few primitive trophoblastic cells that had the potential for forming syncytiotrophoblast only.

It is impossible to give the developmental age of this specimen although the clinical history and endometrial picture suggest approximately 11 to 12 days. The endometrium is perfectly normal and in the twenty-sixth day of the menstrual cycle. The moderate progesterational hyperplasia, consisting of increased secretion and persistent stromal edema, is undoubtedly due to the pregnancy and its direct or indirect effect on the corpus luteum since all pregnant endometrium of this stage shows these features. The hemorrhage within the gland (Fig. 5,B) is within normal limits since it is present in the implantation site of normal early villous pregnancies of 13 to 16 days of age. It is due to the encroachment of the growing trophoblast upon the adjacent glands at a time when the uteroplacental circulation is becoming established.

Whether this pregnancy would have caused the patient to miss her next menstrual period it is impossible to say. The probable resulting lack of chorionic gonadotropic hormone, stemming from lack of cytotrophoblast, makes it unlikely that this patient would have missed her next expected menstrual period. It seems unlikely, however, that were amenorrhea to ensue it would have lasted for more than a few days to a week. In all probability, the patient would then have had a profuse, albeit a somewhat delayed, period but with no definite clinical evidence of pregnancy. Thus this patient, were she a clinical problem, would fall into the ill-defined zone between sterility and infertility. It is interesting to note that in her own obstetrical history she had had five normal children with no abortions. Hence even apparently perfectly fertile patients have their "germ plasm defects" on occasions even though relatively young (31 years of age).

### 3. *Ovum Without Embryo.*—

This specimen (Fig. 6) represents the most common clinical type of pathologic or "blighted" ovum encountered in obstetric practice. Since "blighted" ova, in general, constitute about half of all abortuses examined at the Boston Lying-in Hospital,<sup>12</sup> the present specimen is representative of about 5 per cent of all clinical pregnancies. These abnormal pregnancies tend to abort at about 10 weeks (menstrual age) and often show early hydatidiform degeneration of their villi.<sup>13</sup>

The essential gross features of the specimen are seen in Fig. 6,A and the microscopic details in Fig. 6,B. This ovum, together with those shown in Figs. 8 and 10,B have been previously published.<sup>14</sup> The ovum possessed a polypoid

4,D and E). It is about 4 days of age and was associated with normal eighteenth-day secretory endometrium. It is spherical and the majority of the cells contain only one nucleus each. Furthermore, some of the blastomeres are beginning to show variation in size, shape, and staining reaction. This probably represents early differentiation of trophoblastic cells as compared to those of the definitive embryo. Such a process has been described by Heuser and Streeter for the domestic sow in 1929.<sup>8</sup>

Even though detailed studies on two of the three segmenting ova available in the present series are not complete, it is evident that abnormality at this stage of human development is relatively common. That this should be so follows from Corner's<sup>9</sup> work on the domestic sow. This author showed that of 100 ovulated eggs, only 70 per cent possessed enough normality to reach term. Of the remaining 30 per cent one-third, or 10 per cent, failed to become fertilized even though exposed to spermatozoa, one-third segmented but failed to implant, while the residual one-third implanted but aborted before the fetus reached viability.

It is obvious that patients complaining of sterility may fall into the first two groups, whereas the occasional and/or habitual aborter coincides with the last group. It is interesting that this figure of 10 per cent (one-third of 30 per cent) implanted ova of the domestic sow which are destined to abort is quite comparable to the 10 per cent incidence of spontaneous abortion in the human species.

## 2. *Ovum With Trophoblast Only.*—

This specimen (Fig. 5) is the most abnormal of any implanted human ovum thus far observed. It is characterized by the complete lack of an embryo or chorionic cavity. Even its trophoblastic shell is defective in that the inner cytotrophoblast is absent. The syncytiotrophoblast, however, is present and seems relatively normal in that it invades endometrium, forms lacunae, and erodes maternal blood vessels.

An abnormal ovum was suspected from the appearance of the gross specimen because of the flattening and radial wrinkling of the implantation site (Fig. 5,A). Whether the ovum was better organized and had had more of its normal component parts at some previous stage of development is impossible to say. It seems unlikely, however, that in the segmenting stage any cavity or embryonic cell had been present. It has been shown by Heuser and Streeter in 1941<sup>10</sup> that the syncytiotrophoblast is the first definitive type of trophoblast to form at the embryonic pole after the monkey blastocyst implants on the endometrium, it forming from indifferent polar trophoblast nearest the maternal endometrium. It may be this factor of maternal contact which causes one indifferent trophoblastic cell to become syncytial in type whereas the lack of such maternal environment results in primitive trophoblast forming cytotrophoblast. Whatever the factor responsible, syncytiotrophoblast is the first recognizably differentiated form of trophoblast seen at the implantation pole of the ovum.

What the sequence of events is for the human being at this stage of implantation is unknown. However, the youngest implanted human ovum thus far studied (Hertig and Rock, 1945<sup>11</sup>) shows a transition from the thin meso-

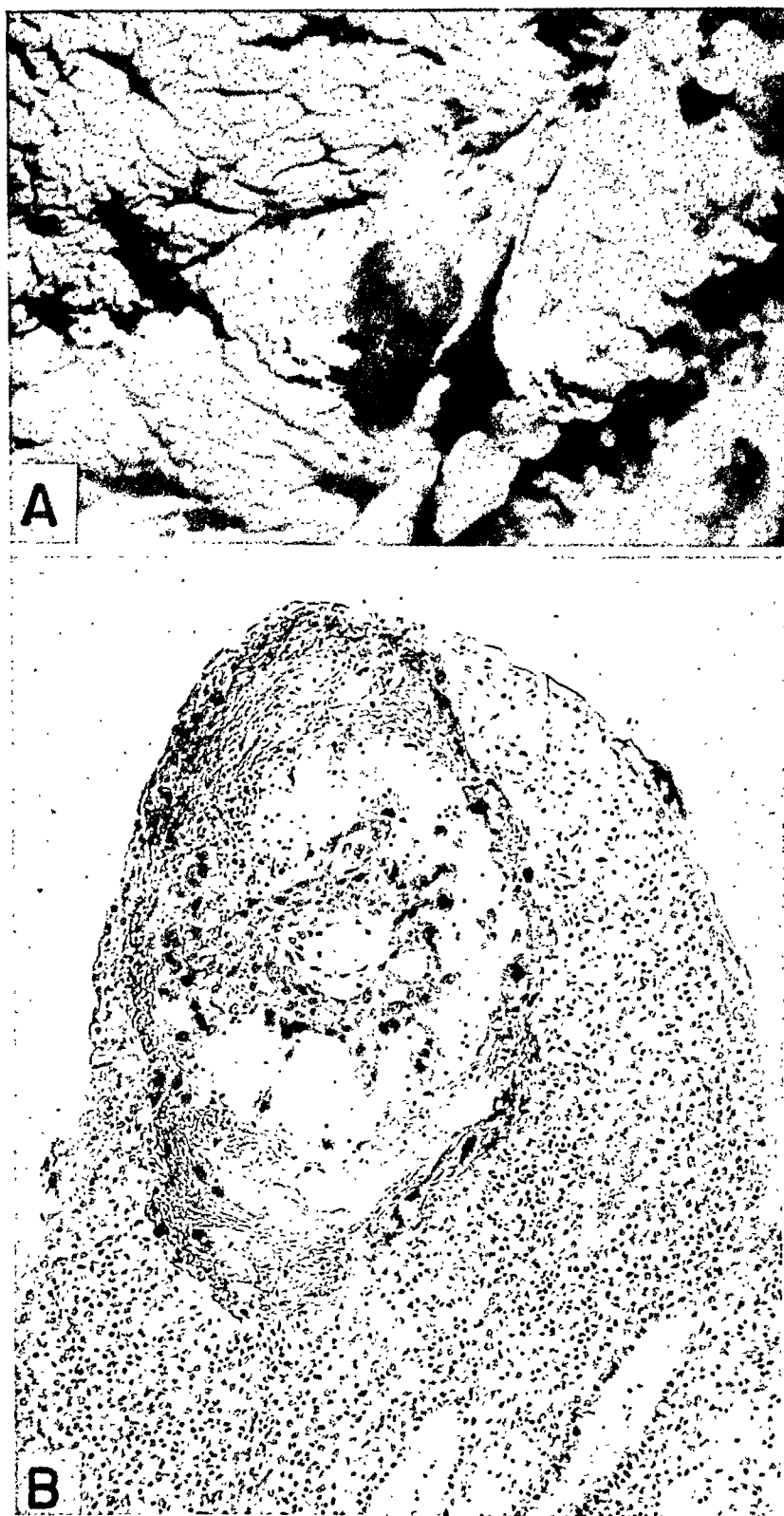


Fig. 6.—An abnormal human ovum, about 13 days, showing a polypoid type of implantation, a poor trophoblast, and no embryo. Carnegie No. 7771.

A, A gross view of the intact implantation site. Sequence 1  $\times$  14.

B, A medium power photomicrograph of the section through the greatest diameter of the ovum. Section 3-4-1  $\times$  100.

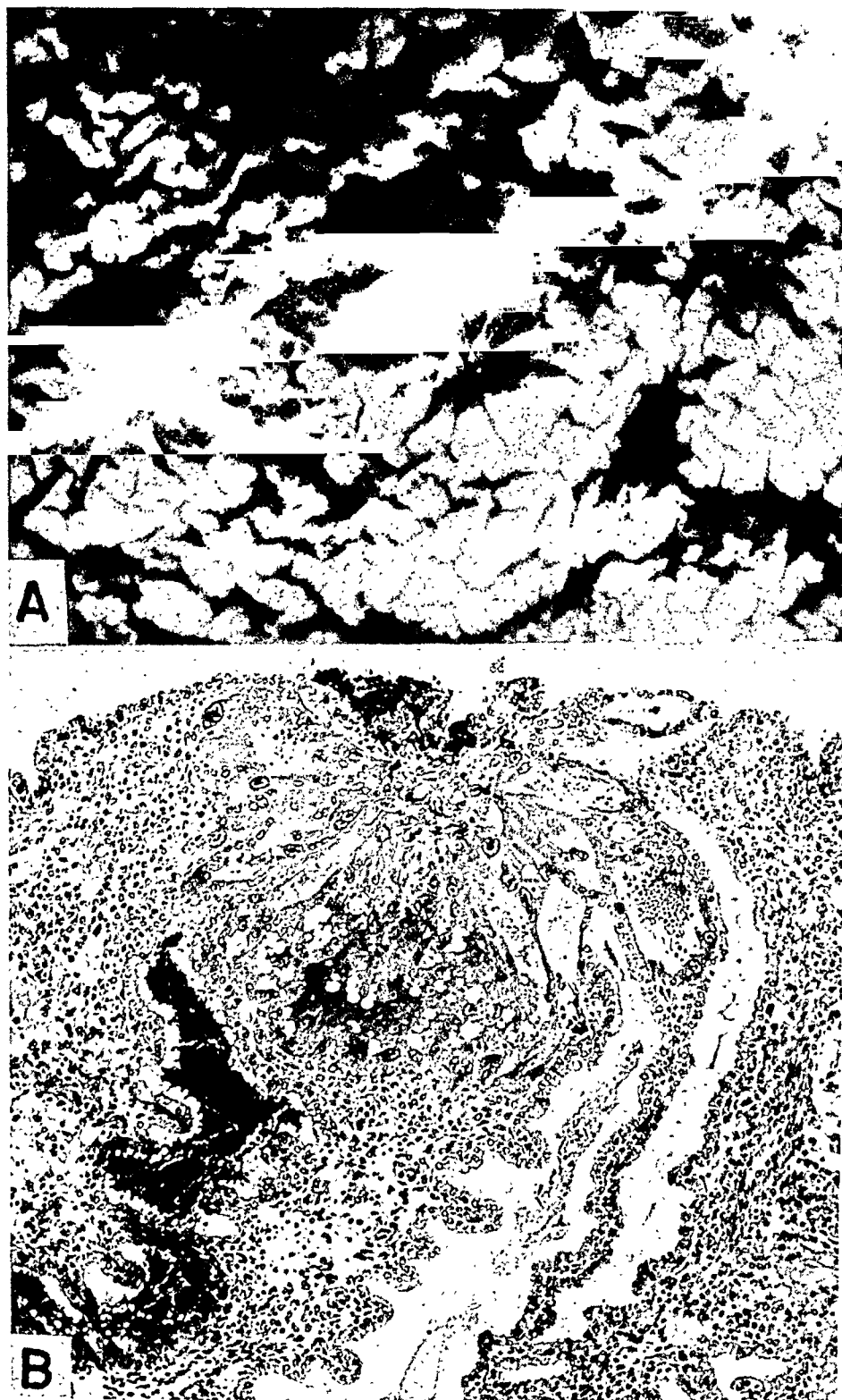


Fig. 5.—An abnormal human ovum, about 11 to 12 days, consisting of syncytiotrophoblast only. Carnegie No. 8329.

A, A gross view of the intact implantation site, photographed under fluid after fixation. Sequence 2  $\times$  22.

B, A medium power photomicrograph of the greatest diameter to show the lack of embryo, chorionic cavity, or cytotrophoblast. Section 13-2-3  $\times$  100.

plantation cannot possibly explain the lack of an embryo within the ovum. It will be recalled that the previous specimen consisting of trophoblast only had a very adequate implantation whereas those shown in Figs. 10,A and B, possessing polypoid or shallow implantation have essentially normal embryos. Hence the poor quality of the present specimen is probably not due to extrinsic factors in the environment but rather to the intrinsic quality of the fertilized ovum itself. Certainly this 36-year-old patient shows no marked degree of clinical infertility with four previous normal children and only one spontaneous abortion.

#### 4. *Ovum Without Chorionic Cavity.*—

This ovum (Fig. 7) is markedly abnormal in that the chorionic cavity is absent for all practical purposes. There is, however, a small amniotic cavity just beneath the curved embryonic disc (Fig. 7,A). The latter is also apparently defective in that no primitive endoderm is observed although the ectoderm is essentially normal. The lack of chorionic cavity accounts for the relatively small size of the specimen although the trophoblast is normal in amount for this stage of embryonic development, i.e., 10 to 11 days. The lack of endoderm and small size of the chorionic cavity—a lineal descendant of the segmentation cavity of the blastula—suggest some primary defect in the primitive trophoblastic shell of the blastocyst since the latter has to do with the formation of both of these structures (Heuser and Streeter<sup>10</sup>). Even though the primitive trophoblast seems to have been abnormal in these respects it was able to form syncytio- and cytotrophoblast in relatively abundant amounts. This tissue, while essentially normal in amount, is poorly arranged. There is a large amount of syncytiotrophoblast at the implantation, or embryonic pole, and a large amount of cytotrophoblast at the abembryonic pole. Thus, instead of these two tissues being concentrically arranged, the syncytio- surrounding the cytotrophoblast, they are more or less laminated. Hence, it would appear that although there is an abundance of trophoblast the primary defect lies within the primitive ancestor of this tissue. The embryo, paradoxically, while originally normal, will probably become increasingly abnormal because of a poor placenta and membranes.

The surrounding endometrium (Fig. 7,B) is normal and in the twenty-fourth day of the cycle. It shows only the usual slight progesterational hyperplasia associated with all early pregnancies of this age.

It is difficult to evaluate this specimen in terms of the clinical outcome of the pregnancy. It is doubtful, however, whether the embryo would have developed into more than a nodular mass of cells within an amniotic cavity. Such specimens, classified in the Carnegie Collection<sup>1</sup> as Pathological Ova, Group IV, consisting of chorion, amnion, and nodular embryo, are one of the most common abortuses seen in clinical obstetrics. It appears impossible to blame the general maternal environment for this defective ovum in view of the normal endometrium and the fact that this 37-year-old patient has had four normal children and only one spontaneous abortion.

type of implantation near the lateral sulcus of the uterine cavity. Grossly, the remainder of the endometrium showed no polyps. Hence it seems unlikely that this ovum just happened to implant on the only polyp present. It is more probable that this type of implantation represents a deviation from the usual type seen in Figs. 2, A and B. Aside from lack of an embryo, the trophoblast itself is of poor quality so that this latter feature may account for a poorly embedded ovum. Regardless of the reason for this feature of the specimen the type of im-



Fig. 7.—An abnormal human ovum of about 11 days without a chorionic cavity. Carnegie No. 8370.

A. A high-power photomicrograph of the embryonic disc and immediately surrounding trophoblast. Note the lack of primitive endoderm (compare with Fig. 2, A). This figure represents the portion of the picture blocked out in Fig. 7, B. Section 6-3-5  $\times$  300.

B. A medium power photomicrograph of the section through the greatest diameter of the ovum and surrounding endometrium. Note the horizontal laminated arrangement of trophoblast (compare with Fig. 2, A). Section 6-3-5  $\times$  150.



### 5. *Ovum With Hypoplastic Trophoblast.\*—*

On the basis of the clinical history and embryonic development, this specimen (Fig. 8) were it normal should be similar to the one shown in Fig. 2,B. However, the trophoblast is extremely defective (Fig. 8,C) and consists of only a small but variable amount of syncytiotrophoblast. At this stage of development the chorion should have well-developed, simply branching villi on the surface. The embryo is essentially normal and possesses a bilaminar germ disc, yolk-sac, and amnion.

The type of implantation is normal for this stage of development and shows maternal hemorrhage (Figs. 8,A and C) exuding from the defect in the overlying decidua capsularis. The endometrium is normal for this stage of pregnancy and shows early decidual reaction around the ovum as well as elsewhere. The massive hemorrhage within the gland beneath the ovum is normal and is analogous to that which exudes from the surface of the implantation site. Such hemorrhage, within the uterine cavity and endometrium adjacent to the ovum, was first described in the Macaque monkey by Hartman<sup>15</sup> on page 45 of his classic monograph and termed the "placental sign." It coincides roughly with the time of the first missed menstrual period. If profuse, it could cause confusion in the mind of the patient with respect to the time of the last menstrual period and hence make it difficult to estimate accurately the expected date of confinement.

The clinical counterpart of this pregnancy has been observed in the Pathological Laboratory of the Boston Lying-in Hospital. Such specimens show a hypoplasia of chorionic development with subsequent bald areas where no villi have developed. This results in insufficient placental tissue to nourish an otherwise normal embryo. The latter then dies, becomes macerated, and the ovum aborts toward the end of the first trimester of pregnancy.

Thus, this 35-year-old patient, who had been perfectly fertile up to this time with four normal pregnancies and no abortions, was destined to have her fifth pregnancy end in miscarriage.

### 6. *Ovum With Malposition of Embryonic Disc.—*

This otherwise normal 12-day ovum (Fig. 9) presents a curious anomaly in the position of its embryonic disc. Ordinarily such a specimen in this stage of development shows the embryo lying more or less parallel with the adjacent trophoblast (Fig. 2,A). This maloriented embryo (Fig. 9,C) probably occupied a normal position earlier because of its normal amniotic development. The amnion has been shown by one of us (A. T. H.) to delaminate in situ from adjacent trophoblast beginning in the 7-day ovum.<sup>16</sup> Hence it appears that this otherwise normal embryonic disc has recently shifted its position due to some unknown factor. Examination of serial sections other than the one here illustrated show that the edge of the germ disc is still attached to the trophoblast in a fashion similar to that shown in Fig. 10,A. It may be that growth of the amnion and chorionic connective tissue mechanically swung the germ disc into this bizarre position by virtue of the attached point acting as a fulcrum or hinge.

\*Two other previllous specimens in this series, Carnegie Nos. 7770 and 7850 show minor degrees of trophoblastic hypoplasia. They are not described in this paper but have been described elsewhere in an earlier publication.<sup>14</sup>

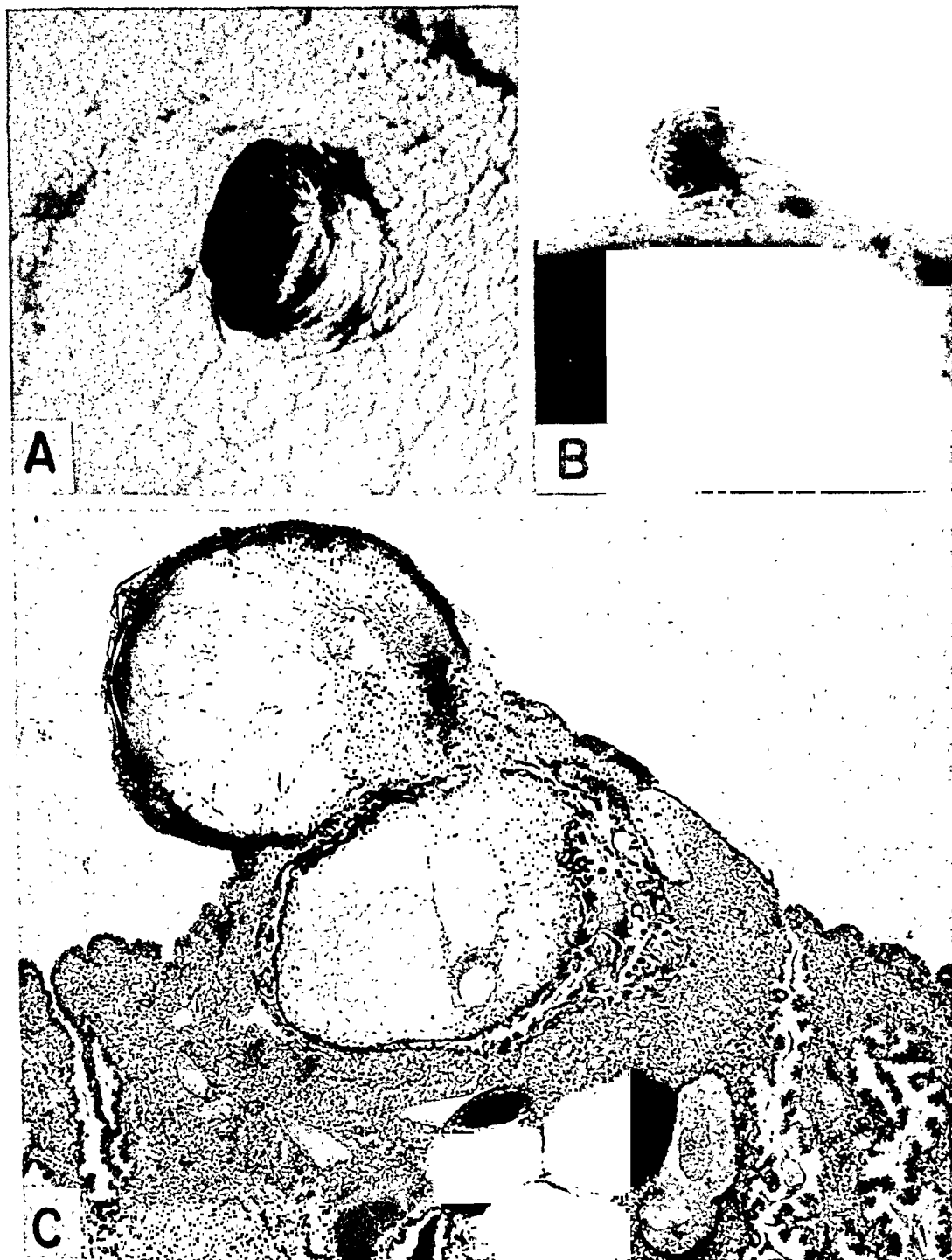


Fig. 8.—An abnormal human ovum of about 15 days showing defective or hypoplastic trophoblast. Carnegie No. 7800.

A, Surface view of implantation site to show hemorrhage. The wrinkled tissue is the surface of the surrounding endometrium. Sequence 2  $\times$  8.

B, Lateral view of implantation site. Sequence 3  $\times$  8.

C, Low-power photomicrograph of section through greatest diameter of the ovum and surrounding endometrium. Note extreme lack of adequate trophoblast. Simple villi should now be present (compare with Fig. 2, B). Section 15-1-3  $\times$  35.

The implantation site, however, is particularly free from evidence of external damage (Fig. 9,A and B) so that operative trauma can probably be ruled out. Also, it should be pointed out that this specimen was removed in the same manner as all the other twenty-eight in our series and only one other (Fig. 10,A) showed anything approaching this curious embryonic anomaly.

Whether this patient would have ultimately aborted or not is impossible to say. It is quite possible that the germ disc would ultimately have freed itself from trophoblastic attachments and become reoriented again in the normal fashion. It is perhaps worthy of note that this 27-year-old patient had had three normal children and one spontaneous abortion previously. The cause of the latter was not determined from her clinical record.

#### 7. *Ovum With Shallow Implantation and Other Anomalies.*—

This early villous ovum (Fig. 10,A), estimated to be about 13 days of age, shows severe deviations from the normal, none of which, either individually or collectively, may necessarily cause abortion. The most striking abnormality is its polypoid type of implantation. The curious buckling of the embryonic disc with a portion of the latter still attached to the trophoblast at the implantation pole of the ovum is nearly as striking. It is interesting and perhaps significant that the trophoblast at the embryonic or implantation pole is poorly developed as compared to its development elsewhere. Early villi are seen nearly everywhere on the surface of the chorion except at the implantation (embryonic) pole where they should be most highly developed. This anomaly of development is perhaps the primary one in the specimen with the probability that the others stem therefrom. Thus, the failure of proper trophoblastic development at the implantation pole may have resulted in the shallow or polypoid type of implantation. This in turn subjects the projecting ovum to mechanical pressure from the opposite wall of the uterus to which the normally implanted ovum is not exposed. At any rate, it appears that the distortion of the chorionic cavity and the buckling of the germ disc could be explained by mechanical pressure on the abnormally exposed ovum. The apparent similarity of the germ disc, in section, to that of a miniature sea horse is amusing. About the only thing one can be certain of with respect to the future of the embryo is that it won't become a sea horse.

Of interest in the clinical history of this 37-year-old patient is that she has given birth to ten normal children but has never had any spontaneous abortions! Whether this pregnancy would have been her first failure is anyone's guess.

#### 8. *Shallow Implantation of Otherwise Normal Ovum.*—

The abnormality of this 12-day specimen (Fig. 10,B) is probably more apparent than real. To be sure it is somewhat more shallowly implanted than others of its general developmental age. However, the excessive hemorrhage from its normally defective decidua capsularis gives it a more polypoid appearance than its depth of implantation would actually warrant. No attempt is made in the illustration to give any microscopic details since the ovum itself is as morphologically normal as the one shown in Fig. 2,A. Certainly the endometrium is as normal as any in the entire series, being in the twenty-sixth day of the menstrual cycle with the usual progesterational hyperplasia.

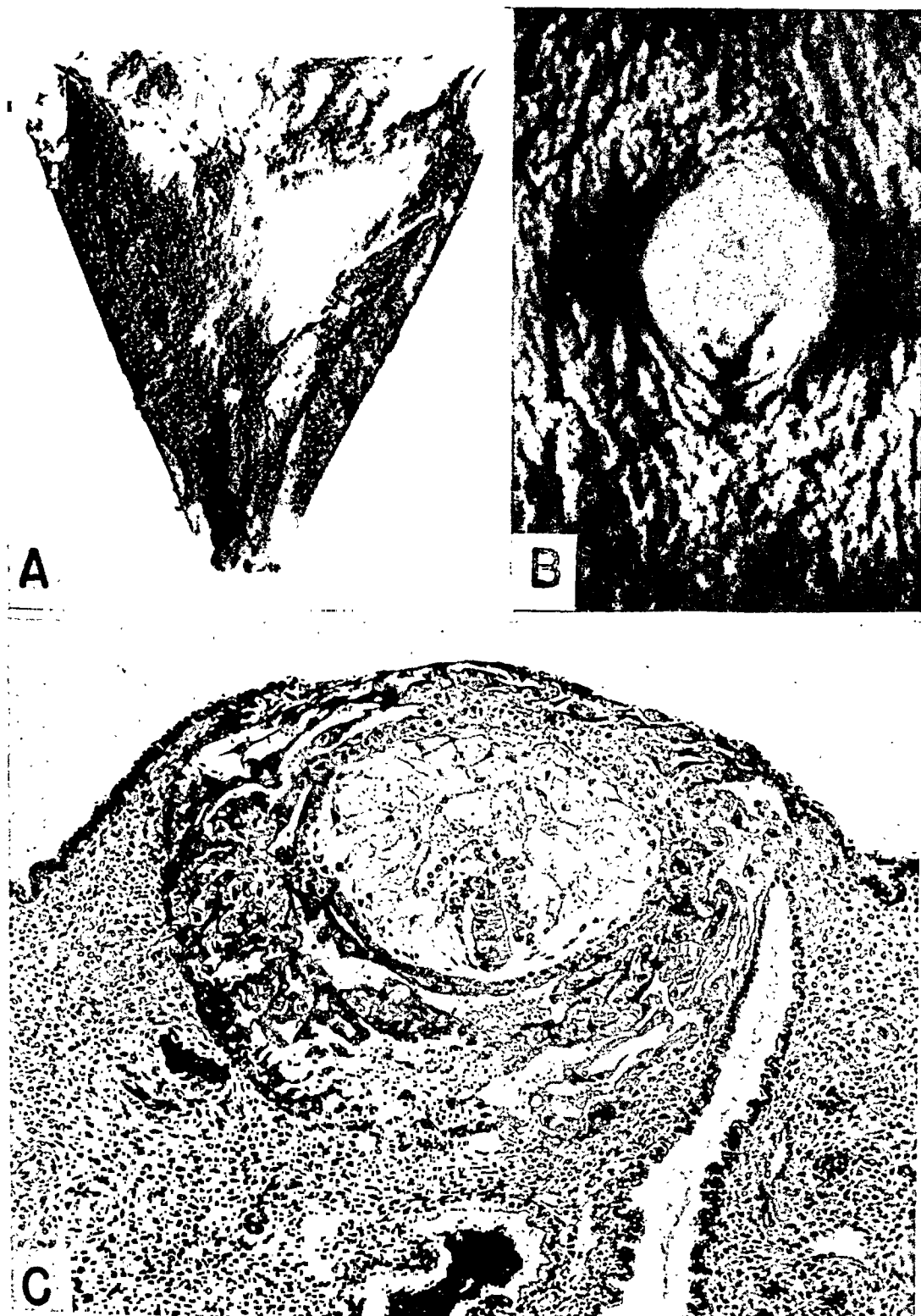


Fig. 9.—An essentially normal 11-day human ovum showing malorientation of the embryonic disc. Carnegie No. 8299.

A, A gross picture of the posterior wall of the uterus showing position and relative size of implanted ovum. Sequence 2  $\times$  1½.

B, More highly magnified view of intact implantation site and surrounding normal endometrium. The defect in the endometrium overlying the ovum is normal. Sequence 4  $\times$  22.

C, A medium power photomicrograph of the section through the greatest diameter of the ovum with adjacent normal endometrium. Note embryo turned on edge (compare with Fig. 2, A). All other parts of the ovum are normal for this stage of development. Section 11-6-5  $\times$  100.

It is doubtful whether this pregnancy would have resulted in abortion. It is, however, possible that such a shallow implantation would have resulted in the formation of a circumvallate placenta. This anomaly of placental development may cause abortion (4.5 per cent of Hertig and Sheldon's series<sup>12</sup>) but many of such specimens go to term. However, during the third trimester of pregnancy the circumvallate placenta may result in premature rupture of the membranes or premature separation of the margin with subsequent onset of premature labor. Clinically this 29-year-old patient gave a history of four normal full-term labors with only one spontaneous abortion.

### Discussion

Of the twelve abnormal ova in the series, ten of which have been described in some detail while the remaining two with slight hypoplasia of the trophoblast were merely mentioned in passing, only seven were destined for probable or certain abortion. These showed defective blastomeres, trophoblast only, absent embryo, absent chorionic cavity, and markedly defective trophoblast, respectively. The remaining five showed minor degrees of trophoblastic hypoplasia, malorientation of the embryo, and various degrees of shallow implantation of the ovum, respectively. These five might or might not have aborted—probably not.

Since only seven of these abnormal pregnancies are definitely destined to abort, the proportion of absolutely defective ova in the series becomes approximately one out of four (seven in twenty-eight). Furthermore, when it is considered that four of these seven (the segmenting ova and the tiny mass of trophoblast) might not have resulted in a clinically evident pregnancy, it becomes evident that the proportion of three definite clinical abortuses out of twenty-five definitely implanted pregnancies (12.0 per cent) is in close agreement with the spontaneous abortion rate of approximately 10 per cent.

Admittedly this series is too small to permit of statistical analysis. However, it was thought advisable to compare such factors as age, number of normal pregnancies, and number of abortions in the histories of the other patients from whom either normal or no ova were obtained.

The age of the patients in each series is not significantly different; those yielding normal ova averaged 33.1 years of age, while those producing abnormal ova averaged 32.5 years. The remainder of these data are shown in Table I.

TABLE I. PREVIOUS NORMAL PREGNANCIES AND ABORTIONS, 136 POTENTIALLY PREGNANT PATIENTS IN WHOM 28 EARLY CONCEPTUSES WERE FOUND (16 NORMAL AND 12 ABNORMAL)

	NORMAL CONCEPTUSES	ABNORMAL CONCEPTUSES	CONCEPTUSES NOT FOUND	ENTIRE SERIES
No. cases	16	12	108	136
Average no. previous preg.	5.62	5.58	4.76	4.94
Average no. previous abort.	0.50	0.83	0.56	0.59
Percentage of previous abort.	9.09%	13.0%	10.6%	10.6%

It is evident that the sixteen patients from whom normal ova were recovered had had, on the average, almost one more previous normal pregnancy

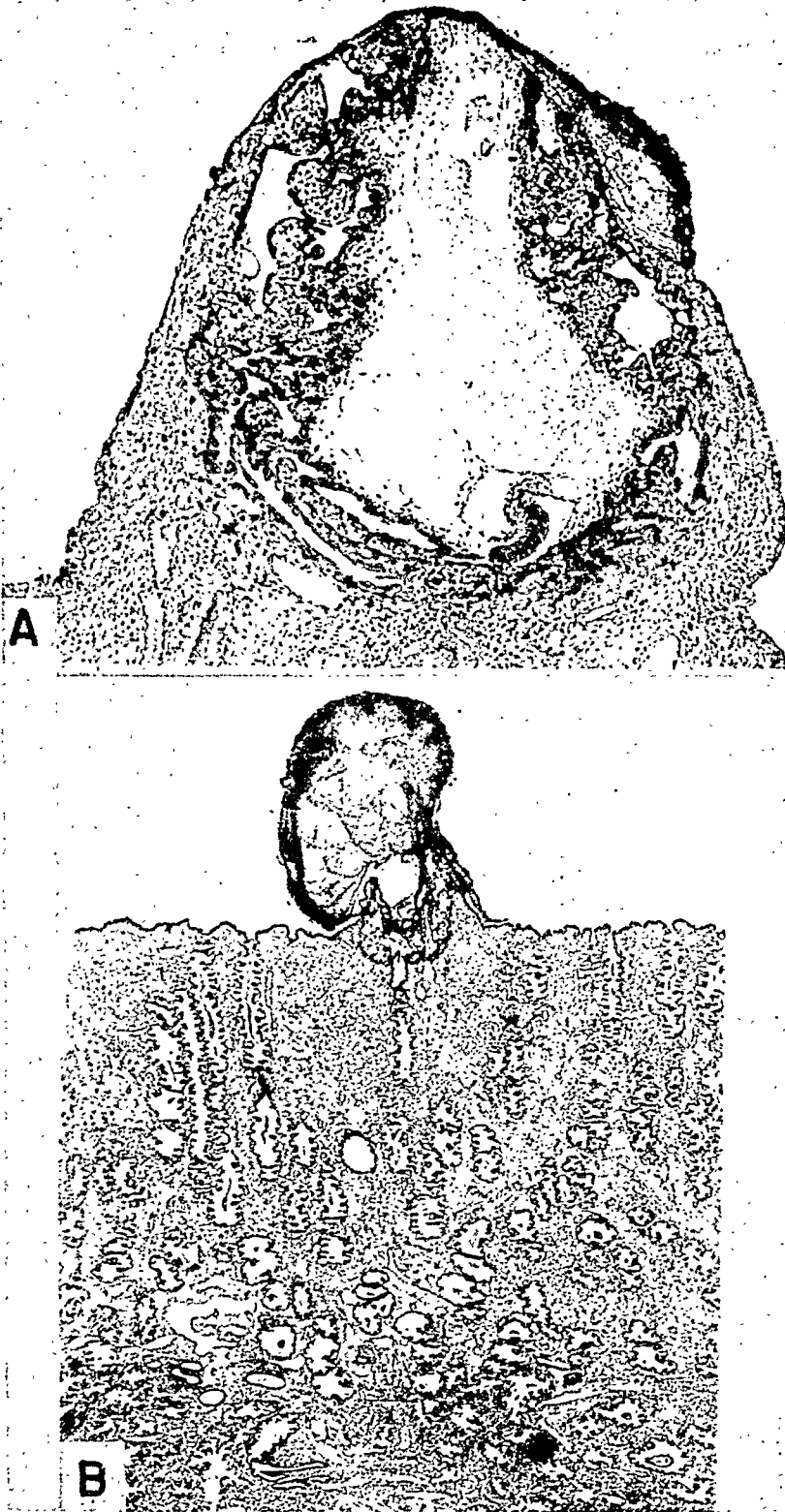


Fig. 10.—Two abnormal human ova showing various degrees of superficial implantation.  
A, An abnormal 13-day specimen showing polypoid implantation, focal hypoplasia of trophoblast at implantation pole, distortion of chorionic cavity, and buckling of the germ disc. Carnegie No. 8290, section 25-2-4  $\times 60$ .  
B, An otherwise normal 12-day specimen showing a somewhat shallow implantation with hemorrhage from the abembryonic pole. (Morphologic details of this stage of human development may be seen in Fig. 2, A.) Carnegie No. 8000, section 11-3-3  $\times 20$ .

## Summary

Over a period of ten years, twenty-eight early conceptuses have been found in a group of 136 potentially pregnant women of known fertility who submitted to hysterectomy for a variety of therapeutic reasons. Twelve of these early human ova were abnormal and of these seven were certainly destined to abort. Four of the latter might not even have caused clinical evidence of pregnancy because of their extreme abnormality.

The ova destined to abort, either with or without evidence of their ability to produce clinical pregnancy, showed such fundamental defects as multinucleated blastomeres, absence of embryonic disc and/or chorionic cavity, or profound hypoplasia of the future placental tissue. None of these patients in whom abnormal ova were found showed any clinical or pathological evidence that maternal environment per se played any part in the production of the abnormal ovum. In other words, the endometrium was normal in all cases. The evidence, such as it is, indicates that the defective fertilized ovum is due to intrinsic "germ plasm" quality rather than to its environment and is the main factor in the production of spontaneous abortion.

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## Discussion

DR. LYMAN W. MASON, Denver, Colo. (by invitation).—The theoretical considerations of this factual presentation are limitless. There are also clinical or practical considerations.

Dr. Mall, as Dr. Hertig has said, was of the opinion that defects in the maternal environment, or faulty implantation, were the cause for the pathological conceptuses which he found. These were usually concerned with evidences of infection and inflammation. His material, mostly spontaneous abortions, was contributed largely by clinicians throughout the country, sometimes with, but frequently without, the attached secundines or decidua. They

than did the 108 patients whose uteri were nonpregnant. The patients who produced abnormal ova, however, did almost as well as the normally pregnant group with an insignificant difference of only 0.04 previous normal pregnancies in favor of the normal group. Moreover, the abnormal group had 0.82 more previous normal pregnancies than did the nonpregnant group. In the matter of previous abortions, the abnormally pregnant group had only 0.33 more than the normally pregnant group and only 0.27 more than the nonpregnant group. Whether these data are statistically significant or not we do not know. The data, however, would appear to indicate a slightly increased fertility in the group normally pregnant as compared to either the abnormally pregnant or nonpregnant group. It is interesting to note, furthermore, that in this entire group of extremely fertile women, one spontaneous abortion had occurred for every 8.4 normal pregnancies (10.6 per cent); the normally pregnant group aborting 9.09 per cent of their previous pregnancies while the abnormally pregnant group had prematurely lost 13 per cent of theirs. These figures, it will be remembered, are very close to the 10 per cent incidence of spontaneous abortion among the pregnant population at large.

In an attempt to determine whether the location of the implantation site of these twenty-five embedded pregnancies within the uterus played any part in the determination of its normality or abnormality, Table II was compiled. It will be recalled that three of the ova were still free in the uterine cavity.

TABLE II. POSITION OF OVA IN UTERUS AND THEIR RELATION TO THEIR CORPORA LUTEA OF ORIGIN

OVA	NO.	POSITION IN UTERUS		CORPORA LUTEA OF ORIGIN			
		ANTERIOR	POSTERIOR	SAME	OPPOSITE	FREE	UNKNOWN
Norm.	16	6	10	10	5	0	1
Abnorm.	12	6*	3*	5	3	3	1

\*The free morulae account for three being on neither the anterior nor posterior wall of the uterus.

It is evident that the normal ova tend to be implanted on the posterior wall whereas the abnormal ones tend to be on the anterior wall although this correlation is by no means absolute. It is interesting that of the first 12 specimens found, this correlation was absolute.<sup>3</sup> Dr. William E. Studdiford, in commenting on this apparent fact, pointed out that the series was too small to allow any conclusions. It is still too small for generalization but the trend, as stated, is still apparent.

With respect to the side of the uterus on which the ovum implanted in relation to its corpus luteum of origin there appeared to be no correlation, as can be seen in Table II, for approximately one-third of each series embedded on the opposite side of the uterus. In no instance, however, were any ova, either good or bad, found below a line drawn halfway between the fundus and lower uterine segment. Therefore, at least none of these pregnancies were destined to be complicated by placenta previa.



I am sure that it is the general belief that the study of these extremely early conceptuses, which has been presented today by Drs. Rock and Hertig, has advanced us much along the road, at the end of which lie the answers to the "whys" and the "hows" asked by those who concern themselves with the problems of human reproduction.

DR. KARL WILSON, Rochester, N. Y.—I desire to refer to a case of a 12-day ovum. It was obtained accidentally in an endometrial biopsy and we have the whole ovum. It looks quite normal. It appears that this defect through which the ovum was implanted ought to be healed over now and whether that represents a potential abortion it is difficult to say. The high-power view of the embryo shows a very early yolk sac. (Fig. 1.) Fig. 2 shows the endometrium in which the ovum was implanted. My first impression was that there was too much edema here and I was wondering if that would indicate that this ovum would have perished anyway because of defective endometrium. If that were true it would indicate that abortion would occur. The patient menstruated normally two days after the biopsy was obtained. Whether she would have menstruated and cast off the ovum or whether the menstrual flow was due to loss of the corpus luteum one can hardly say.

DR. THADDEUS MONTGOMERY, Philadelphia, Pa.—This presentation has again raised the old question of the relative influence of heredity and environment in the production of congenital abnormalities and congenital disease.

The phenomena which are sometimes observed in binovular pregnancy would seem to have a possible bearing on the answer to this problem. For instance, one oftentimes finds within the content of the womb, in which the environment may be assumed to be uniform, a binovular pregnancy in which one fetus and placenta are quite normal and the other degenerated and dead. Occasionally there is also encountered a binovular pregnancy in which one pregnancy has undergone hydatidiform degeneration and the other is apparently a normal pregnancy.

However, in contradiction to this point of view, there are some cases reported in which apparently chorionepithelioma has followed a full-term pregnancy and apparently has arisen from retained bits of chorionic tissue and syncytium rather than from the elements of a new pregnancy. It is quite possible, therefore, that both heredity and environment play an important role in these early disturbances of placentation and embryonic development.

DR. D. PLASS, Iowa City, Ia.—I would like to raise the question as to whether the evidence presented proves that this is a genetic responsibility. The mere fact that the endometrium appears normal is not proof that the cells are functioning normally. I doubt very seriously whether this evidence would prove acceptable to a biologist for that reason. We are learning more and more that one cannot link morphology and function with any accuracy.

DR. ROCK (Closing).—Dr. Hertig will perhaps in closing tell us the average age of patients we worked with because it may be that in these women a larger proportion of eggs were already a little older than are those still fertile ova of postadolescent women in general. It has been shown in the guinea pig and rabbit that with increase of ovulation age of eggs the incidence of abortion increases. I would suppose that in like manner eggs, older because of the age of the woman herself, are probably more likely to abort. Certainly the incidence of abortion increases after the age of thirty-five years. It has been shown also in some of the experimental animals that fertilization with older spermatazoa—that is, sperm out of the testicle longer than in normal ejaculates—is very likely to accomplish abnormal fertilization or fail to activate the egg at all. Thus we may have defects arising from within the zygote itself.

Some very interesting work has been done by Chang in Pincus' laboratory in Shrewsbury on the effect on the conceptus of the time of its arrival in the uterus. If a fertilized rabbit egg, 2 days of age, is placed in the uterus of another normal rabbit the day before ovulation, it will fail to establish pregnancy. Chang did this work, using dozens of eggs, and concluded from percentage results that if a 2-day fertilized rabbit egg is placed in a rabbit just at

were of all ages, none so young, of course, as those which have been presented today. One cannot escape the belief that many, if not most, of these inflammatory changes were post-abortual, rather than the cause for the pathological conceptuses which were found.

The opposing viewpoint, viz., that the abnormal conceptuses are caused by defects inherent in themselves, has been presented today, on material which is much more significant. The case has been made increasingly strong for this viewpoint, especially by the work of Corner on the domestic sow, in which abnormal conceptuses are found side by side with normal ones in the same environment. Dr. Hertig has called attention today to the fact that in the cases shown, the endometrium was normal. One is impressed by the ten per cent mentioned by Dr. Hertig. This is the incidence which seems to run through all abortions, in human beings as well as that found by Corner in the sow. Must we accept this ten per cent of abortions as inevitable?

If one accepts pathology in the conceptus as due to faults inherent therein, and if we reject Mall's belief in maternal environmental defects as a cause, then it logically follows that attempts to save so-called "threatened abortions" are destined to failure, since they represent, not the beginning of trouble, but the end of a damaging process which is already past hope.

Also, it seems quite probable that cases of occasional menorrhagia and lengthened menstrual intervals in women whose menstrual cycles are usually normal, usually followed by a period marked by increased discomfort and increased flow, may well represent abortions of conceptuses such as have been described by Dr. Hertig.

Whether the fault is intrinsic in the conceptus, or is secondary to defective maternal environment, little has been accomplished in determining the fundamental cause of the pathological changes observed in the conceptus.

In the study of sterility, with which the presentation of Dr. Rock and Dr. Hertig is directly concerned, some progress has been made in semen specimens as a whole, based upon Dr. W. W. Williams' original work with bulls, but little as yet upon the individual sperm, which appear normal morphologically, although here we have millions to compare with each other in the same specimen. The problem is much more difficult for the relatively rare egg, fertilized or otherwise, which is recovered.

Considerable has been accomplished in studies along embryonic and genetic lines in some of the plants, and in some of the lower animal forms, especially in the *Drosophila* and *Paramecium*. It has been found that there are genelike bodies, apart from those in the chromosomes, in the cytoplasm, which may undergo mutations, and thereby profoundly alter the reactions of the cells to other tissue cells and to each other. These characteristics are transmissible through the cytoplasm of the cells, and not the chromosomes. Some of these mutations can be made to occur, and controlled to some extent. Such has been shown to account for a susceptibility to carbon dioxide in some *Drosophila*, for a certain type of male sterility in corn, and for defects in the plastids of some of the green plants which cause them to lack chlorophyll. It may be that environmental factors, physical or chemical, as yet unrecognized, are the cause of such mutations, temporary so far as the individual is concerned, involving only certain ova or spermatazoa, giving rise to products of fertilization which are abnormal. It may be possible, therefore, that environmental factors may not entirely be ruled out by the microscope, but may lie beyond what can be seen. One can not see in the microscope, for example, the causes for an allergy which must represent altered cells in tissues, which may suddenly appear in an individual never before affected.

In a long interest in sterility, with which the subject of abortion forms an integral part, from my own observations, from all I have read, and from all I have heard, I do not think that either of these fundamental concepts of spontaneous abortion has been proved to the entire exclusion of the other. In Hertig's and Rock's cases, there were maternal factors, which admittedly justified hysterectomies, in spite of normal-appearing endometrium, and hysterectomies are not done by outstanding gynecologists for minor indications. It must also be remembered that by the time the conceptus reaches the uterus, it is not a sperm or an ovum but a morula, composed of many cells, which has been subjected to environmental factors from the time of fertilization and before.

ovulation there will be a somewhat smaller number of abortions but it is still almost 100 per cent. If, however, the 2-day fertilized egg is put in a two-day postovulatory rabbit then the percentage of normal conception rises; and if it is put in a four to six-day postovulatory rabbit the percentage of pregnancies again decreases. We have no way of knowing whether or not our abnormal conceptuses arrived in the uterus at the proper time. I think it is possible that sometimes we may attribute to the zygote the defect that we should attribute to tubal function or tubal fluid for, as Dr. Plass has stated, we know practically nothing of what the conceptus demands of the endometrium.

Dr Montgomery brought up the question of how do we get in binovular twins one bad and one good one. How can we attribute this to the fault of environment when here we have two eggs in the same environment? It might be explained on the time of arrival of those eggs in the uterus because a variation of only two days of either arrival or implantation might make all the difference in the world.

DR. JOSEPH BAER, Chicago, Ill.—I would like the essayist in his closing remarks to tell us something about the occurrence of genes in the cytoplasm.

DR. HERTIG (Closing).—Dr. Mason has raised the point as to whether this inflammatory-like infiltration of the leucocytes had some etiologic relationship to abortion. Dr. Mall, while a very eminent embryologist, apparently did not realize that all spontaneous abortions have as part of their final morphologic picture thrombosis, necrosis, and hemorrhage in the decidua. The leucocytic response to sterile necrosis is what he interpreted as inflammation. This is seen whether the corpus luteum is surgically removed or whether there is a blighted ovum or low-implanted ovum as the basis for the abortion. As to Dr. Mason's second point that threatened abortions are inevitable, I do not agree. About half of them do not abort irrespective of what is done. There is, however, a group of threatened abortions which without proper treatment will abort but can theoretically be salvaged by treatment. This is the relatively small group amounting to about 30 per cent of all abortuses or 15 per cent of threatened abortions. These potentially salvageable threatened abortions have normal embryos and chorions that are living at the time the patient is first seen. The presence of this group in a series of abortuses and hence in any series of patients who threaten to abort is the explanation for the increased salvage of threatened abortion by administration of estrogens.

With respect to Dr. Wilson's specimen, it is unique to get a normal ovum properly sectioned with the significant parts of the embryo in it from chance biopsy material. We have one such specimen at about 8 days which appeared to have been completely removed by biopsy, also, as in this case, in a sterility patient. That brings up the question of when is the best time to do an endometrial biopsy in sterility patients, and we feel it should be at the onset of menstruation or prior to implantation when it is difficult to damage a free-floating blastula. The yolk sac which Dr. Wilson mentioned is a beautiful early stage in the formation of this structure. Since nothing is known in its early formative period, this specimen promises to be unique. We had hoped for years to find an early yolk sac in the process of examining the uteri from these patients. The edema of the endometrium is probably within normal limits. Nobody can answer whether withdrawal of the chorionic support caused the patient to have her period within two days or whether she would have had it anyway. I think the ovum is a normal one. Dr. Wilson also asked whether the implantation site at the top should not have closed; in the normal 11- to 13-day ovum it is not really healed but is closed over by what Graf von Spee called "Schlussoogulum."

With respect to Dr. Schwarz' question, the implantation pole of the ovum is almost invariably determined by the position of the embryo itself. In the rare case when that is not so and the ovum implants upside down, then one has a membranous insertion of the cord. What determines why the ovum should stick itself in the position it does is not known except that it implants with the embryonic pole toward the endometrium. The ovum itself may be sticky or there may be present some difference of electrical potential which attracts the embryonic pole to the endometrium.



Fig. 1.—Early ovum of about 11 days.

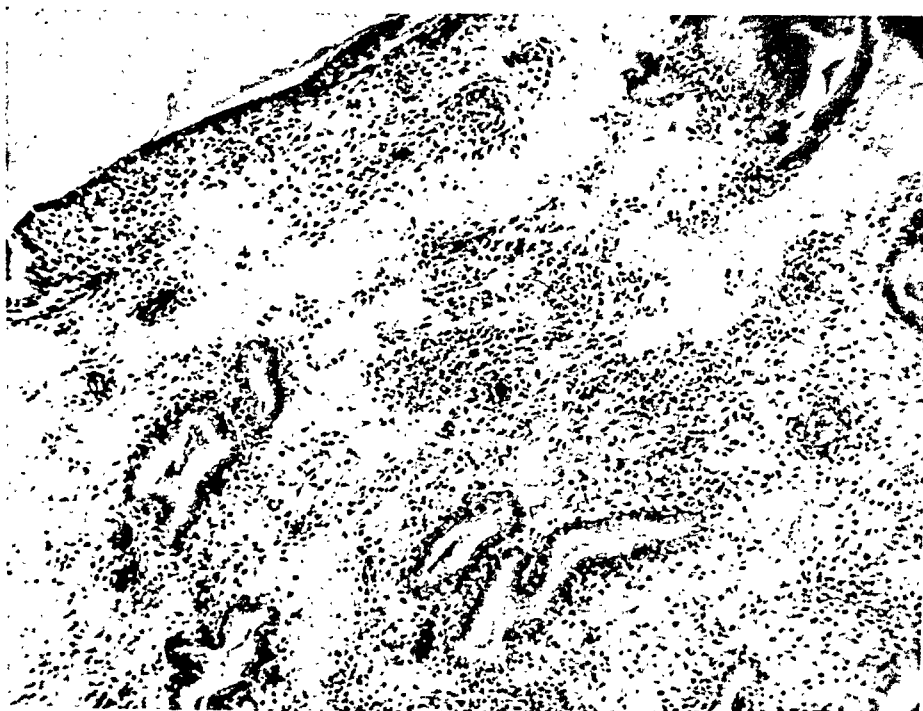


Fig. 2.—Edematous decidua.

# THE INFLUENCE OF DIETHYLSTILBESTROL ON THE PROGRESS AND OUTCOME OF PREGNANCY AS BASED ON A COMPARISON OF TREATED WITH UNTREATED PRIMIGRAVIDAS\*

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Medical School)*

THIS is a report of continued progress in the clinical evaluation of our concept concerning the action of diethylstilbestrol in human pregnancy. The basis for the use of diethylstilbestrol in pregnancy and the evidence for its progesterone-stimulating effect have been reviewed in a previous publication,<sup>1</sup> a clinical study in which the drug was shown to be beneficial in the treatment of threatened abortion and in the prevention of abortions that would have been anticipated because of previously lost early gestations. A preliminary report was also included on the use of stilbestrol for the prevention of late pregnancy complications in patients in whom pre-eclampsia, eclampsia, premature delivery, or stillbirth was anticipated because of their past medical or obstetrical histories. A larger series of such patients is being reported elsewhere.<sup>2</sup> Certain difficulties are encountered, however, in the evaluation of results in patients of this sort. In evaluating the results of stilbestrol therapy for threatened and chronic abortion, we had reliable figures on the spontaneous cure rates of these conditions as a basis for the analysis of our data. No such generally accepted figures are available, so far as we know, as a basis for evaluating any prophylactic therapy against complications of late pregnancy. It was for this reason that the present study was undertaken, the plan being to compare the late pregnancies of treated primigravidas with those of synchronous control primigravidas in order to determine whether the drug might have value in reducing the usual incidence of late pregnancy complications and fetal loss. Although the incidence of toxemia, premature delivery, and stillbirth in primigravidas has been extensively worked up in most obstetrical clinics, there is always the possibility that differences in prenatal care, dietary conditions, seasonal variations, etc., might influence results. In order to eliminate all possible variables it was deemed important to have a synchronous control group from the same clinic rather than to depend upon the data from previous years or from other clinics.

We have shown<sup>3</sup> that late pregnancy toxemia, premature delivery, and death of the fetus in utero are preceded by a premature deficiency of estrogen

\*Presented at the Seventy-Second Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 16 to 18, 1940.

I do not know much about the problem of binovular twins. We do know that we see normal twins along with abnormal ones. I have always felt that these mummified twins did not have as good blood supply as the others; their placentas are normally formed but often infarcted.

As to the point made about hydatidiform mole subsequent to normal pregnancy, I consider that to be a new pregnancy which has undergone hydatid degeneration. I feel that the chorionepitheliomas which follow normal pregnancy are the result of retained trophoblast which has undergone malignancy, but why that happens I do not know.

Dr. Plass's question whether these things are genetic has been answered by Dr. Rock: we do not know. It was our purpose to point out that here was a group of normal patients, 10 per cent of whose implanted ova were abnormal in the presence of an apparently normal environment.

The average age of these patients was 32.5 years in the group producing abnormal ova, and 33.1 years in those producing normal ova.

I think Dr. Rock's point about the time of arrival of eggs in the uterus is well taken and that may account for Dr. Mall's classic observation on the abnormality of the majority of ova in ectopic pregnancy because they certainly implant in an environment which is not normal and at a time when they should not be implanted in that location.

In answer to Dr. Baer, I know nothing about the genes within the nucleus. I can only say that these embryologic observations are in the "horse and buggy" phase of morphology; they have not been studied histochemically. We were content to find the ova and get serial sections made of them.

get the right dosage. In handling a large number of clinic patients it was felt that the use of two sorts of pills might lead to bad errors in dosage. The schedule was therefore modified. One-half of a 25.0 mg. tablet (12.5 mg.) was taken daily during weeks 12 and 13 and a whole tablet (25.0 mg.) daily during weeks 14, 15, and 16. At the start of the seventeenth week the dosage was increased to 50.0 mg. and maintained at this level through the twentieth week. It was then raised to 75.0 mg. for weeks 21 through 25, 100.0 mg. for weeks 26 through 30, and 125.0 mg. for weeks 31 through 35, when it was discontinued. When treatment was started after the twelfth week the initial dosage was always the one for the particular week of pregnancy when therapy was begun. This is dosage schedule No. 1, which was followed in the treatment of the first 152 primigravidas who, with 283 synchronous control primigravidas, comprise Series A (v.i.).

The schedule just described was employed in a number of abnormal patients in another study,<sup>2</sup> whose urinary pregnanediol was being followed by the method of Venning. In many of these cases the curves flattened out or even dropped towards the end of a five-week interval at one dosage level, instead of showing the normal gradual rise found in other patients taking gradually increased doses of stilbestrol. Therefore, the schedule was changed so that one and one-half of the 25.0 mg. tablets, 37.5 mg., were ingested daily during weeks 16, 17, and 18; two tablets, 50.0 mg., during weeks 19, 20, and 21; two and one-half, 62.5 mg., during weeks 22, 23, and 24; 75.0 mg. during weeks 25 and 26; 87.5 mg. during weeks 27 and 28; 100.0 mg. during weeks 29 and 30, 112.5 mg. weeks 31 and 32, 125.0 mg. weeks 33 and 34, and 137.5 mg. during the thirty-fifth week. In this manner (schedule No. 2), 235 primigravidas were treated. They and 272 synchronous control primigravidas comprise Series B (v.i.).

With the exception of an occasional complaint of nausea or itching of the skin, no toxic effect could be attributed to the stilbestrol as administered. In no instance was the drug discontinued or the dosage changed because of symptoms, despite which fact the symptoms disappeared. There were no deaths among the treated or control mothers of this study.

### Comparisons Between Treated and Control Primigravidas

An over-all comparison of the incidence of late pregnancy complications is graphically presented in Fig. 1. According to statistical analysis,\* the better total results among the treated patients in each category are significant, highly so as regards the incidence of toxemia and fetal mortality.

#### 1. *Toxemia of Pregnancy.*—

TABLE I. INCIDENCE OF LATE PREGNANCY TOXEMIA

	SERIES A		SERIES B	
	TREATED	CONTROL	TREATED	CONTROL
Total no. of cases	152	283	235	272
Pre-eclampsia Grade I	5	18	3	12
Pre-eclampsia Grade II	0	2	1	5
Eclampsia	0	0	0	1
Totals	5 (3.3%)	20 (7.0%)	4 (1.7%)	18 (6.6%)
Totals A + B	Treated:	9 (2.3%)	Control:	38 (6.8%)

In Table I the incidence and type of toxemia are summarized. Throughout the rest of this paper, italics indicate statistical significance of the difference

\*We are indebted to Jane Worcester, Dr.P.H., Assistant Professor of Biostatistics at the Harvard School of Public Health, for advice in the statistical analysis of our data and for a review of the final manuscript to check its statistical accuracy.

and progesterone. We have also presented evidence that this hormonal deficiency, once established, may be part of a vicious cycle in which lack of hormonal support, vascular deficiency, and toxin formation augment one another and that any one of these factors, unless corrected, may eventually lead to all three.<sup>3</sup> The high incidence of late pregnancy complications in primigravidas as compared with multiparas has been ascribed rather generally to mechanical factors that might cause a relative deficiency in blood supply to the uterus. Our studies have indicated<sup>3</sup> that any situation which affects adversely the blood supply to the uterus will interfere with the normal production and metabolism of the placental steroid hormones, estrogen and progesterone. The combined action of estrogen and progesterone, on the other hand, is characteristically one of increased myometrial and vascular growth. By the administration of stilbestrol and provision thereby of an extra stimulus for the production of estrogen and progesterone, we would not expect completely to avert all late pregnancy complications in all primigravidas but, if our concept is correct, the onset of such complications should be postponed, their severity reduced, and, in a certain proportion of patients who would ordinarily have no trouble until late in pregnancy, entirely prevented.

### The Clinical Experiment

This study was carried out at the Boston Lying-in Hospital.\* It was begun in April, 1947, and ended Jan. 1, 1949. A record was kept of all primigravidas who made their first visit before the twentieth week of gestation and whose condition was diagnosed as normal. No patients with known essential hypertension, diabetes, or nephritis were included. So far as was possible under the circumstances, alternate patients were interviewed and given stilbestrol.† A calendar dosage schedule was made out for each patient and written instructions were provided. The patient checked the calendar each day after taking her pills and was interviewed at each visit to be sure she understood the instructions and was faithful about taking the medication as prescribed. At the end of therapy, after thirty-six weeks, all left-over pills were returned and counted in order to obtain a further check as to whether or not instructions had been followed.‡ In all other respects there was no difference in prenatal care between the treated and control patients, nor was there any significant difference in their ages. Ninety-two to 93 per cent of both groups were under 30 years of age when first seen. The administration of stilbestrol was started between the twelfth and sixteenth weeks in 75 per cent of the treated cases and by the twentieth week in the remainder.

The drug was taken orally. In the dosage schedule originally recommended by us<sup>1</sup> (and still felt to be the closest to physiological) the amount taken is increased by 5.0 mg. at weekly intervals after the fourteenth week. This involves the use of 5.0 mg. tablets to supplement the 25.0 mg. pills in order to

\*The authors are indebted to the medical and nursing staffs of the Boston Lying-in Hospital for their cooperation in making this study possible. Indispensable assistance and advice were given by Drs. Duncan E. Reid, William J. Mulligan, Arthur W. Tucker, Jr., and Samuel B. Kirkwood in the matter of abstracting records and checking on the diagnoses. We are indebted to Drs. Clement A. Smith and Stewart H. Clifford for advice in organizing the data on premature infants. The secretarial work involved and the all-important task of interviewing the patients, dispensing stilbestrol, getting back surplus pills, etc., etc., were performed by Mrs. Grace M. Harris, to whose perseverance and tact may be attributed the unusual cooperation of the patients in following instructions. She was assisted by Ethel Stewart, R.N., to whom we are also indebted for abstracting records. Tabulation of the data from the record abstracts as fast as they were received was performed by Mrs. Muriel G. Mann, thereby considerably simplifying the final task of the authors.

†E. B. Smith & Sons supplied the 25.0 mg. tablets of stilbestrol used in this study.



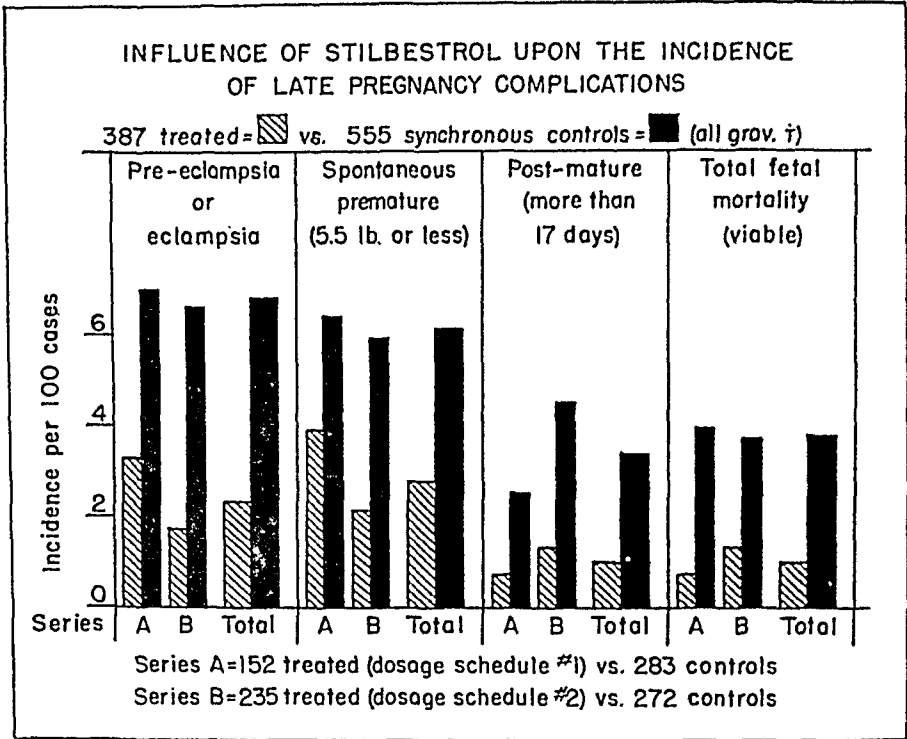


Fig. 1.

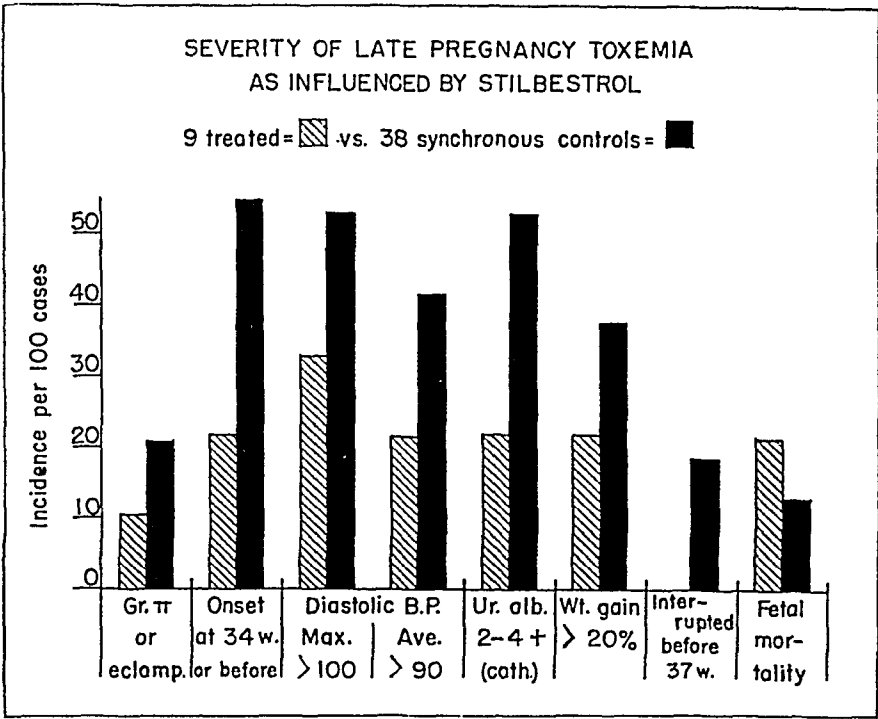


Fig. 2.

between control and treated cases. These figures show not only less toxemia on stilbestrol but also a reduction in the incidence of pre-eclampsia Grade II\* and eclampsia, from 1.6 per cent in the 555 controls to 0.26 per cent in the 387 treated patients. In other words, what toxemia did occur was less severe.

In Fig. 2 the nine cases of toxemia among the treated patients are compared with the 38 cases among the controls. From a statistical point of view in such a comparison, it is unfortunate that we have only nine cases of toxemia among the treated patients. Despite the fact that such a small number of cases is not subject to statistical analysis, the data in Fig. 2 suggest that even pre-eclampsia Grade I in these nine women was less severe and later in its onset than it might have been if stilbestrol had not been taken. There were only two in whom the disease had its onset prior to the thirty-fourth week, as against over half of the 38 cases of toxemia in the control group. Toxic signs were also less severe in these nine patients. In none of them was the interruption of pregnancy indicated prior to two weeks before term; whereas in three control cases cesarean section had to be resorted to at 32 and 36 weeks, and in four others labor was artificially induced at 32, 35, 36, and 37 weeks, respectively, because of the increasing severity of toxemia (the case of interruption at the thirty-second week being in an eclamptic).

There were two fetal deaths in the nine toxic pregnancies that occurred despite stilbestrol treatment, as against five fetal deaths in thirty-eight patients with toxemia in the control series. Both of the fetal deaths in the stilbestrol-treated patients were associated with extenuating circumstances. One of the two women presented her first toxic signs (hypertension and albuminuria) at 21 weeks, after she had been on stilbestrol for only five weeks. Although she was clinically normal at her only previous visit at 16 weeks, when stilbestrol was started, it seems probable, considering the very early appearance of toxic signs and their persistence after delivery, that this patient had antecedent renal disease and should not have been classified as a normal primigravida. Even if this was a case of true toxemia, stilbestrol administration was not prophylactic, since, according to our experience in studying such cases,<sup>3</sup> the hormonal deficiency of toxemia is underway some four to eight weeks before the disease is clinically detectable. We have shown<sup>4</sup> that stilbestrol administration alone is of no value for the definitive treatment of established pre-eclampsia. This patient is also the only one of the 387 treated primigravidas who developed signs and symptoms diagnosed as Grade II pre-eclampsia. At 30 weeks she went into labor spontaneously and delivered a macerated, stillborn infant.

The other fetal death among the nine cases of toxemia on stilbestrol was in a patient who had pyelitis starting at 26 weeks and who discovered that the drinking of much tea preliminary to her prenatal visits was a means of obviating hospitalization. Her diluted urine contained less protein according to the qualitative test used in the clinic. Her ingenuity in this respect, together with her uncooperative attitude, made us suspect that she may not have taken her stilbestrol, despite the accuracy with which she marked her medication sheet and the fact that she returned the right number of pills when her pregnancy was completed. In addition to pyelitis she developed hypertension consistent with a diagnosis of pre-eclampsia Grade I, and at 32 weeks she delivered spontaneously a 3 pound infant which lived only three days.

## 2. Spontaneous Premature Delivery.—

According to the accepted definition of prematurity<sup>5</sup>—any child born alive weighing 2,500 grams (5½ pounds) or less—the total incidence of this abnormality was 2.8 per cent in the treated cases as against 6.1 per cent in the controls (Fig. 1).

\*Throughout this paper the term "pre-eclampsia Grade II" refers to severe pre-eclampsia or preconvulsive toxemia, whereas "pre-eclampsia Grade I" refers to mild pre-eclampsia.

TABLE IV. DISTRIBUTION OF LENGTHS AT BIRTH IN PREMATURELY DELIVERED INFANTS  
(OF COMPARABLE GESTATIONAL AGES—OMITTING TWINS)

CROWN-HEEL LENGTH AT BIRTH	STILBESTROL		CONTROLS	
18 inches or less	7	17%	19	33%
18 $\frac{1}{8}$ to 18 $\frac{7}{8}$ inches	4	10%	12	20%
19 inches or more	30	73%	27	47%
Totals	41		58	

TABLE V. DISTRIBUTION OF INITIAL WEIGHT LOSSES IN PREMATURELY DELIVERED INFANTS  
(OF COMPARABLE GESTATIONAL AGES—OMITTING TWINS)

WEIGHT LOSS IN PER CENT OF BIRTH WEIGHT	STILBESTROL		CONTROLS	
7% or less	12	29%	11	19%
7.1 to 11.0%	25	61%	29	50%
More than 11.0%	4	10%	18	31%
	41		58	

As shown in these tables and graphically depicted in Fig. 3, stilbestrol-treated women not only lost none of their babies but also had fewer babies which were actually premature in the matter of weight (Table III) and length (Table IV). Moreover, more of their babies were able to suckle, and to leave the hospital with their mothers. That the greater weight of more of their babies might have been due to water retention from exposure to larger amounts of steroid hormones seems hardly tenable, since fewer of these offspring lost over 11.0 per cent of their birth weight during the early days of extrauterine life (Table V).

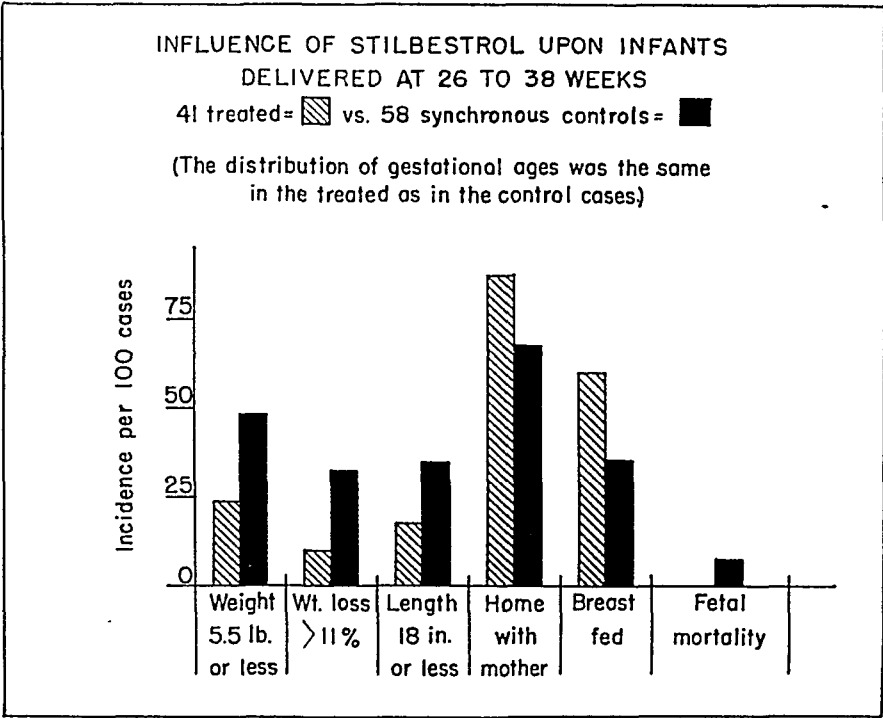


Fig. 3.

Scattergrams were made (Figs. 4 through 7) in order to see how the values for the weights and lengths of the premature infants of treated and control mothers fell in relation to curves based on averages. In these scattergrams

An important observation in this group of patients is the fact that if prematurity is defined on the basis of the expected date of confinement rather than of birth weight there is no difference between the treated and control groups. Among the 387 treated patients there were 42 (including one who had twins), or 10.8 per cent, whose only complication was spontaneous delivery more than two weeks before term. In the control group of 555 cases there were 66 such patients (including three who had twins), or an incidence of 11.8 per cent. In our first study,<sup>1</sup> stilbestrol administration was associated with a 33 to 47 per cent reduction of premature delivery in those who had previously delivered early. It was pointed out, however, that over 50 per cent of the women who had previously delivered early, regardless of how many times this had happened, did not carry to term on stilbestrol, although the fetal loss from prematurity was greatly reduced. It was inferred that in over half of these women factors other than hormonal were primarily responsible for this late pregnancy complication, the hormonal deficiency being a part of the end result and therefore a final contributory factor only. The findings in the present study suggest that factors other than hormonal account for most of the premature deliveries in primigravidas.

Despite the failure to reduce spontaneous premature delivery in primigravidas, as defined in terms of gestational age, medication with stilbestrol proved of real benefit to the infants of these women. There were nine deaths among the 69 infants of the control group whose only complication was spontaneous delivery more than two weeks before term, a mortality rate of 13 per cent. None of the 43 babies of the treated patients who delivered early died.

In order to determine the cause for this strikingly beneficial influence of stilbestrol upon fetal salvage, the data on babies who were of comparable gestational age in the two groups were analyzed. In this analysis all twins were omitted, since there were more twins in the control than in the treated groups. (This excluded one of the fetal deaths in the controls.) In Series A there were five of the controls who gave birth between the twenty-fifth and thirty-second weeks. Since none of the treated women in Series A delivered during this interval, these five controls (and their four fetal deaths) are also omitted from the comparisons. The distribution of gestational ages in the remaining data analyzed is shown in Table II. The omission of infants that would weight the data unfairly against the prematurely delivered offspring of the controls resulted in a similar distribution of gestational ages in the two groups, and therefore a fair basis for the comparison of babies delivered prematurely with and without stilbestrol therapy. These are the cases that were used in compiling the statistics for Tables III, IV, and V, and for Fig. 3.

TABLE II. DISTRIBUTION OF GESTATIONAL AGES IN DATA ANALYZED FOR FIG. 3 AND TABLES III, IV AND V

		TREATED		CONTROLS	
Total number of babies		41		58	
Week of delivery	26 to 28	1	2.4%	1	1.7%
	30 to 32	1	2.4%	2	3.5%
	32+ to 34	3	7.3%	4	6.9%
	34+ to 36	9	22.0%	13	22.3%
	36+ to 38	27	66.0%	38	65.6%

TABLE III. DISTRIBUTION OF BIRTH WEIGHTS IN PREMATURELY DELIVERED INFANTS (OF COMPARABLE GESTATIONAL AGES—OMITTING TWINS)

WEIGHT AT BIRTH	STILBESTROL		CONTROLS	
5 pounds, 8 ounces or less	10	24%	28	48%
5 pounds, 9 ounces to 6 pounds, 9 ounces	23	56%	23	40%
6 pounds, 10 ounces or more	8	20%	7	12%
Totals	41		58	

twins only are omitted. The upper curve in each of these four charts was determined by Ylppö in 1919 and the lower by Scammon and Calkins between 1922 and 1925.<sup>6</sup> Over 90 per cent of the premature infants of the treated patients fell above the upper curves for both weight and length. The scattergrams of control babies, on the other hand, are not significantly higher than the 50 per cent above and 50 per cent below average that would be expected if the upper curves of Ylppö are applicable to babies delivered at the Boston Lying-in Hospital between April, 1947, and January, 1949, the period of this study.

It seems clearly indicated by the above data that the administration of stilbestrol as a prophylactic measure reduces fetal mortality from prematurity largely because the infants are unusually mature for their gestational ages. In other words, it would appear that a better intrauterine environment had been provided than would have pertained if stilbestrol had not been given. Our interpretation would be that the placental secretion of estrogen and progesterone had been stimulated to its maximum capacity up to the time when nonhormonal factors gained the supremacy and brought on the vascular and hormonal deficiency associated with the onset of labor.<sup>3</sup> According to our present state of knowledge concerning the physiological action of the placental steroid hormones, the combined action of estrogen and progesterone in adequate amounts would be required to accomplish this result.

### 3. Postmaturity.—

Delivery seventeen or more days after the expected date of confinement occurred in nineteen, *3.4 per cent*, of the control women, with one fetal death, and in four treated women, *1.0 per cent*, with no fetal loss.

### 4. Unexplained Stillbirths.—

Six infants, *1.1 per cent*, were stillborn to control mothers; two, *0.5 per cent*, to treated mothers. The incidence of this abnormality was very low in both groups and the difference is not significant. Stillbirths that occurred in patients who had pre-eclampsia or eclampsia were considered referable to toxemia and included in that category. All fetal deaths in both control and treated patients that were due to obstetrical accidents (e.g., subarachnoid hemorrhage, strangulation by cord about neck or prolapse of cord) were omitted from this study.

### 5. Total Fetal Mortality.—

In the control primigravidas, five infant deaths were associated with maternal toxemia, nine with prematurity, and one with postmaturity; six were stillborn, making a total of twenty-one, *3.8 per cent*. The deaths of two infants of treated mothers were referable to toxemia; two other babies were stillborn, totalling four, *1.0 per cent*.

### 6. Uncomplicated Pregnancies.—

A. *Mothers*: The uncomplicated gestations of the remaining 330 treated primigravidas were compared with those of the remaining 426 controls to discover whether there were any differences accountable to the administration of stilbestrol. These comparisons included the highest diastolic blood pressure reading during the last month of pregnancy, percentage gain in weight from the time of the first visit, percentage loss of weight after delivery, the duration of the first and second stages of labor, and the incidence of uterine bleeding at term, uterine inertia, and postpartum hemorrhage. No significant difference between treated and control mothers was found in any one of these categories.

B. *Infants*: An unexpected development of this investigation has to do with the weight and length of the babies born to the women who received stilbestrol and had normal gestations. In the first study<sup>1</sup> mention was made of the observation volunteered by several obstetricians that the premature babies from

Figure 4

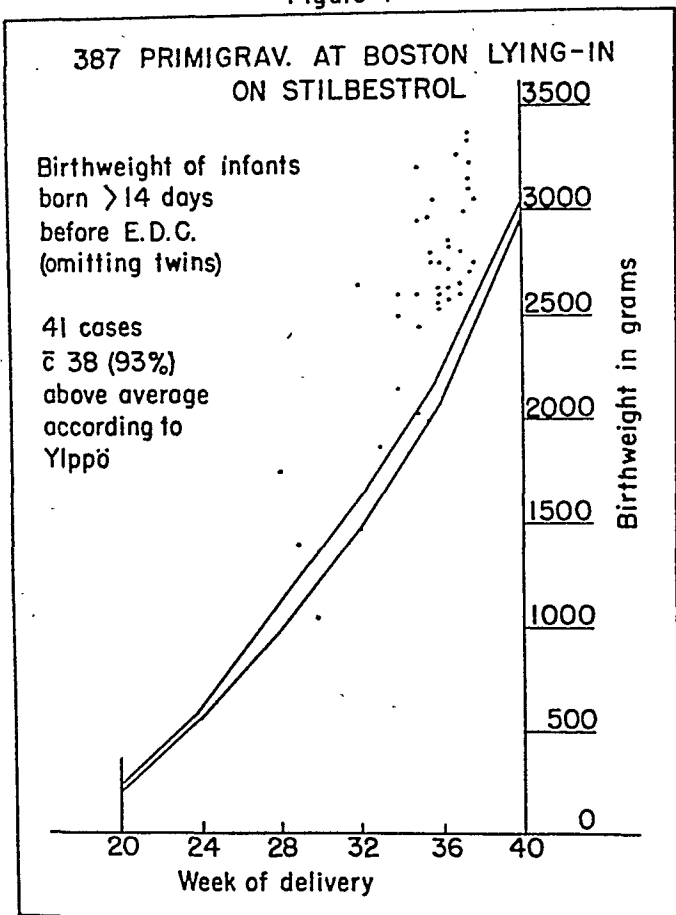


Figure 5

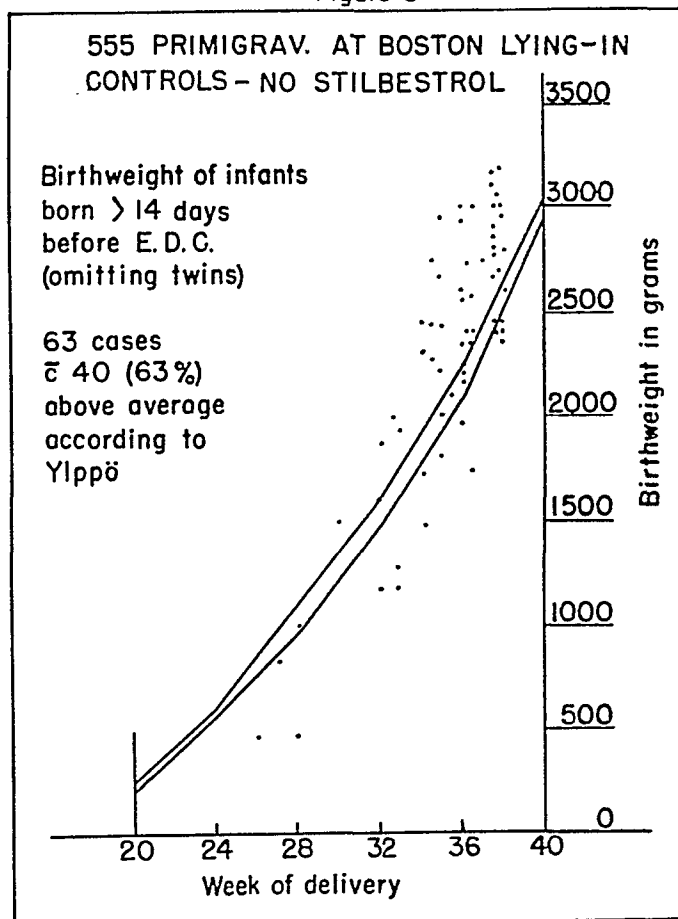


Figure 6

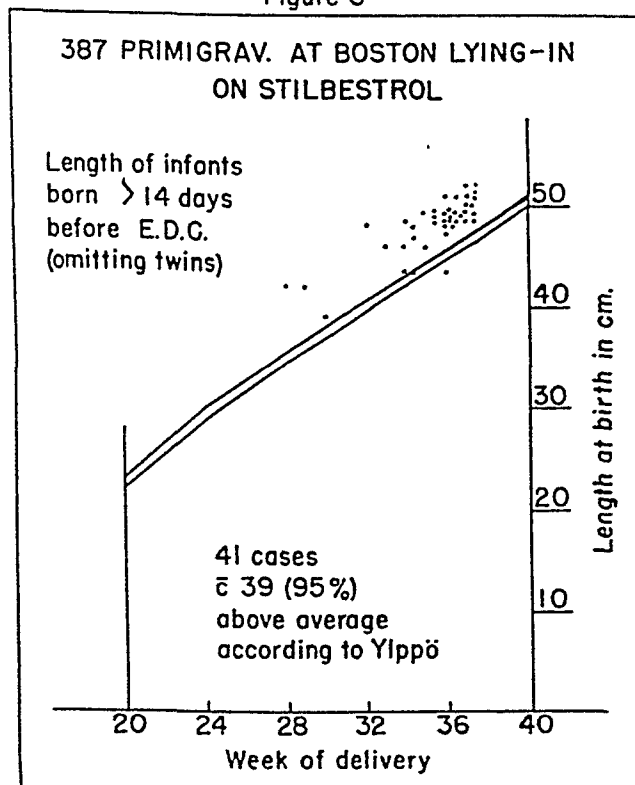
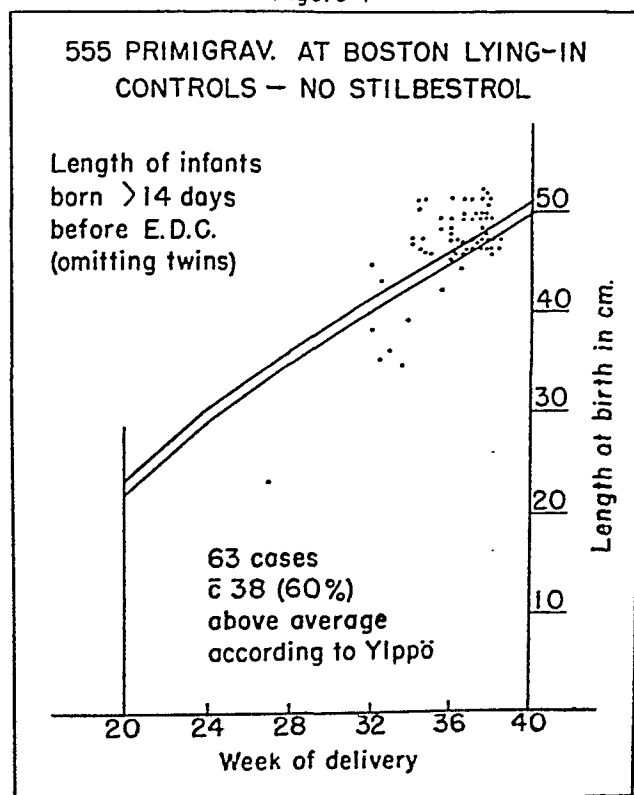


Figure 7



infants of the population as a whole.<sup>7</sup> In the present study, one of 387 "stilbestrol" babies had an anomaly, polydactylism; whereas seven of the 555 controls were abnormal, as follows: polydactylism 2, meningocele 2, mongolism 1, hydrocephalus 1, and anencephalus 1. We know of no reason why stilbestrol, started as late as the twelfth week, should reduce the incidence of fetal abnormalities, as might be inferred from these figures. It seems safe to conclude, however, that the use of stilbestrol in the dosages prescribed by us is associated with no risk of maintaining an abnormal conceptus. Moreover, there has been no case (among the total of 1,191 stilbestrol-treated patients in our records) where malignant change in the chorionic elements has occurred, although a number of the abortuses have had hydatidiform degeneration.

### Summary

In a clinical experiment aimed at determining the value of diethylstilbestrol in the prevention of the complications of late pregnancy, 387 primigravidae women in the prenatal clinic at the Boston Lying-in Hospital were given the drug in gradually increasing doses from the early part of pregnancy (weeks 12 to 20) to the thirty-sixth week. So far as was possible, alternate primigravidae women who presented themselves for prenatal care before the twentieth week were treated, the synchronous untreated patients, of whom there were 555, serving as controls. Except for stilbestrol administration, the obstetrical care of the two groups was identical.

The incidence of late pregnancy toxemia was very low (2.3 *per cent*) in the stilbestrol-treated patients. The difference between this figure and the 6.8 *per cent* incidence in the control series could not have occurred by chance. In the few cases that developed despite stilbestrol, the disease was later in onset and less severe than in the control group.

Analysis of the data on spontaneous premature delivery revealed that the premature infants of stilbestrol-treated mothers were unusually large and mature for their gestational ages. If prematurity is defined in terms of weight of the babies, the incidence of this abnormality was significantly less in the treated patients than in the controls. On the basis of week of delivery, on the other hand, there was no real difference between the two groups.

Postmaturity was significantly less frequent in the stilbestrol-treated patients than in the controls.

The incidence of unexplained stillbirth was 1.1 *per cent* in the controls and 0.5 *per cent* in the treated patients. This difference could have occurred by chance.

There were four fetal deaths in the stilbestrol-treated patients, an incidence of 1.0 *per cent* as against twenty-one, or 3.8 *per cent*, in the untreated patients; a highly significant difference. This reduction in fetal mortality would appear to be due largely to two factors: (1) the lower incidence and later onset of toxemia, and (2) the greater size and maturity of prematurely delivered infants.

A complete analysis of the data on the uncomplicated term pregnancies of the treated and control patients revealed no difference so far as the mothers were concerned (e.g., length of labor, uterine inertia, intrapartum or post-

stilbestrol-treated patients were unusually rugged for their gestational age. Direct evidence in support of this observation has been given above. The explanation appears to be that the drug stimulated better placental function and hence bigger and healthier babies by the time premature delivery occurred. Although stilbestrol was expected to keep more gestations normal, as demonstrated by the material already presented in this paper, we did not anticipate that it could render normal gestation "more normal," as it were. The babies of these treated mothers, however, gave evidence of having been in a better maternal environment, as shown in Tables VI and VII, which compare the weights and lengths of those infants concerning whom these figures were available. There were significantly fewer light infants and significantly more heavier and longer infants.

TABLE VI. DISTRIBUTION OF BIRTH WEIGHTS OF FULL-TERM INFANTS

WEIGHT AT BIRTH	STILBESTROL		CONTROLS	
5 pounds, 9 ounces to 5 pounds, 15 ounces	12	4%	30	8%
6 pounds to 6 pounds, 15 ounces	77	25%	112	31%
7 pounds to 7 pounds, 15 ounces	146	47%	161	43%
8 pounds or over	76	24%	66	18%
Totals	311		369	

TABLE VII. DISTRIBUTION OF LENGTHS AT BIRTH OF FULL-TERM INFANTS

CROWN-HEEL LENGTH AT BIRTH	STILBESTROL		CONTROLS	
Less than 19 inches	16	5%	18	5%
19 to 20 inches	103	35%	177	49%
20 to 21 inches	112	37%	120	33%
More than 21 inches	67	23%	47	13%
Totals	298		362	

That the greater size of more stilbestrol infants was real and not referable to retention of fluid is demonstrated in Table VIII. The initial loss of weight was exactly the same in each group.

TABLE VIII. DISTRIBUTION OF INITIAL WEIGHT LOSSES IN FULL-TERM INFANTS

WEIGHT LOSS IN PER CENT OF BIRTH WEIGHT	STILBESTROL		CONTROLS	
8% or less	64	21%	81	22%
8+ to 11%	139	46%	166	46%
11+ to 15%	74	25%	92	25%
More than 15%	26	8%	26	7%
Totals	303		365	

Seventy per cent of the babies of both groups were breast fed, showing that stilbestrol administration during pregnancy, in the dosages given, had no influence upon lactation. The fact that a greater number of premature infants of stilbestrol-treated mothers were breast fed than of the controls, therefore, must have been referable entirely to the state of the infants.

The question as to whether stilbestrol might salvage a greater number of abnormal fetuses has logically arisen, the greatest concern being for defective ova that would ordinarily abort. In our first stilbestrol study,<sup>1</sup> 491 of the 632 cases reported were started on stilbestrol for threatened abortion or for the prevention of abortions that might have been anticipated. Three hundred and ninety-five of these carried to viability with one fetal abnormality, a case of webbed fingers. This gives an incidence of only 0.25 per cent as against the 1.0 per cent incidence of congenital deformities and abnormalities in newborn



use of other drugs which are not necessarily hormones but which act directly upon the vascular apparatus.

We owe a great debt to Dr. Olive Smith and Dr. George Smith for this stimulating study which represents a prodigious amount of work and a great deal of careful thought.

DR. OLIVE SMITH, Brookline, Mass. (by invitation).—Dr. Page has suggested that the results presented could be entirely explained on the basis of a direct effect of stilbestrol on the vascular supply to the placenta. We find it impossible to sidestep the issue as easily as this, first because we have good reason to believe that estrogen alone in the dosages given could not possibly produce the vascular and myometrial development reflected in the results obtained, and second because recent developments in the measurement of the urinary metabolites of progesterone are confirming our original evidence for the stimulative effect of stilbestrol upon the production of progesterone in human pregnancy.

Drs. Davis and Fugo have recently confirmed our original observation that stilbestrol administration in pregnancy is followed by an increased excretion of sodium pregnandiol glucuronide as measured by the Venning method. They have shown, however, that no rise in pregnandiol excretion after stilbestrol is demonstrable when this metabolite of progesterone is measured on hydrolyzed urine by the  $H_2SO_4$  color reaction. Dr. Marrian of Edinburgh using essentially this same method has reported an actual decrease in pregnandiol following stilbestrol. Drs. Davis and Fugo have jumped to the conclusion that the rise in sodium pregnandiol is due to recovery not of more pregnandiol but of stilbestrol glucuronide. This possibility was considered by us some years ago when Mazur and Shore recovered stilbestrol glucuronide from the urine of stilbestrol-treated rabbits. It was rapidly eliminated on three scores: (1) Sodium pregnandiol glucuronide recovered from the urine of patients taking 150 mg. of stilbestrol daily was added to the urine of surgical castrates, hydrolyzed, and extracted by methods known to recover stilbestrol. The estrogenic activity has amounted to no more than 50 rat units per 100 Gm. of sodium pregnandiol glucuronide. In terms of stilbestrol glucuronide this would represent 15 micrograms per 100 mg. of sodium pregnandiol glucuronide, too little to have any effect at all upon pregnandiol values. (2) The administration of 75 to 100 mg. of stilbestrol daily to non-pregnant patients results in no pregnandiol excretion as measured by the Venning method. (3) We have emphasized the fact that stilbestrol alone is of no value in the definitive treatment of established toxemia, our explanation being that syncytial degeneration once under way is irreversible. As much as 200 mg. of stilbestrol daily does not prevent the steady decrease in the excretion of sodium pregnandiol that characterized both this disease and the termination of normal pregnancy.

The difference between the results by the Venning method and by the color reaction on hydrolyzed urine, therefore, cannot be explained on the basis of recovery of stilbestrol glucuronide. Some other explanation must be found.

Dr. Marrian has isolated pregnanolone from human pregnancy urine as a glucuronide. Dr. Venning reports that pregnanolone is recovered by the Venning procedure and constitutes about 20 per cent of the sodium pregnandiol of pregnancy urine. Dr. Dorfman of Cincinnati demonstrated it in the urine of a man to whom progesterone was given, thus establishing it as an excretory product of progesterone. For the past year we have been trying to put all of these facts together as they may apply to the effect of stilbestrol upon the excretion of estrogen metabolites. On 100 urine specimens from ten different women taking stilbestrol during pregnancy we have measured pregnandiol by three different methods: the Venning method and two modifications of the  $H_2SO_4$  color reaction on hydrolyzed urine, the second of which is our own and eliminates some of the non-specific chromogens that will give gross overestimates in certain pregnancy urines when this colorimetric test is used. As a result of this study we can make the following statements at this time:

By all three methods an increase in pregnandiol excretion immediately follows the administration of stilbestrol to a patient whose pregnandiol level is just beginning to drop, i.e., a patient in the very early stages of a progressive progesterone deficiency.

partum bleeding, weight gain). Analysis of the data on full-term infants, however, revealed that significantly more babies of stilbestrol-treated mothers weighed over eight pounds and were more than 21 inches long at birth.

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### Discussion

DR. ERNEST W. PAGE, San Francisco, Calif. (by invitation).—The use of stilbestrol for the prevention or treatment of disease has brought to our specialty one of the most exciting and controversial topics in recent years. Dr. Olive Smith and Dr. George Smith have been among the most astute students and assiduous observers in this field for over fifteen years. Now they present us with a method for rendering a "normal" process "more normal" by the use of stilbestrol. Even though hormones, vitamins, and enzymes are all catalysts which accelerate vital biochemical reactions and therefore have much in common, it is difficult to believe that such a potent drug as stilbestrol will prove to be—like an essential vitamin—necessary for the most successful outcome of normal pregnancies. This point, however, is only philosophical and is not an argument for or against the concept.

The observations presented here have passed the cold scrutiny of a biometrician, and the differences noted, especially in the occurrence of pre-eclampsia and in the size and weight of the premature infants, are hardly within the realm of chance. Two questions remain for discussion; one concerns the "randomness" of sampling and the other concerns the interpretation of the results.

Is it possible that some unconscious factors of selection could have operated in the production of these differences? Does the fact that the control sample is 43 per cent larger than the experimental sample indicate that whatever disturbance occurred in the planned alternation of cases might likewise have disturbed the complete "randomness" of selection? This can be answered only when the experiment is repeated and the results are confirmed by some persistent iconoclast.

But let us now accept these rather startling statistics as wholly valid and consider the concept. Dr. Smith has always emphasized the purely endocrinologic effects of stilbestrol, namely, that it stimulates the placenta to utilize more chorionic gonadotropin and thereby to produce more estrogens and more progesterone. I would like to point out that it may not be necessary to evoke such a concept in order to explain the results. Dr. Smith has referred several times to a secondary disturbance of the blood supply to the pregnant uterus as a factor in producing many of the accidents of pregnancy. It would seem to me that the vascular disturbance is more likely the primary cause for the impaired placental function, for the smaller babies, and for pre-eclampsia. Could not stilbestrol be a drug which exerts its effect directly upon the vascular apparatus and thereby reduces the frequency of ischemia of the gravid uterus? With this as a basis, we may circumvent the objections of some endocrinologists who, correctly or not, claim that stilbestrol does *not* increase the secretion of progesterone, and that an endocrine organ does *not* use a protein hormone during its elaboration of steroids. Most investigators have had the experience of following what later may prove to be erroneous concepts, but still arriving at valid conclusions.

If stilbestrol can prevent interferences with the blood supply to the pregnant uterus, we have not only a rational basis for its use, but a stimulus to investigate the prophylactic

DR. RALPH REIS, Chicago, Ill.—The Drs. Smith have given us a very comprehensive picture of the effect of stilbestrol on the pregnant woman and have placed it above the realm of chance. The results show more big babies, fewer premature babies, longer babies, and heavier babies. I must confess at the moment to a degree of bewilderment because with the previous recommendations of the more or less prophylactic use of stilbestrol in diabetics who are pregnant will we not defeat the very purpose and means by which we hope to salvage babies from the pregnant woman who is diabetic? If we give them stilbestrol and they develop larger and heavier and longer babies, where will we end up with our treatment of the diabetic pregnant woman?

DR. GEORGE W. KOSMAK, New York, N. Y.—I would like to have the essayist state what dosage of stilbestrol he uses.

DR. FRED L. ADAIR, Chesterton, Ind.—In connection with this remarkable contribution of the Drs. Smith I want to ask about the effect of the administration of stilbestrol on the placenta from two points of view: the normality of the placenta and the size of the placenta. Both of these might have a direct influence on the development of the fetus. Also, it seems to me that in view of the fact that the placenta and some of its physiologic activity may be related to toxemia of pregnancy, there might be an indirect influence of stilbestrol upon the functioning capacity of the placenta and its normality.

A number of years ago Dr. Hulda Thelander and I studied the relationship between the placental and fetal weight and we found that the volume of the placenta was more important than either the dimensions or weight; that there was a closer relationship between the volume of the placenta and fetal weight than there was between dimensions or actual weight of the placenta. In considering the relationship between the placental and fetal size, volumetric studies by means of fluid displacement would be more valuable than either the weight or dimensions of the placenta.

DR. WILLIAM J. DIECKMANN, Chicago, Ill.—The work of the Drs. Smith may prove to be a most important contribution. Their results, presumably due to the administration of stilbestrol, are better than we have been able to accomplish by extensive and expensive prenatal care. I do not know what it is due to. I hope that they will continue their work, to obtain a much larger series, and I also hope that other obstetricians who have large clinic services will undertake this work. As soon as we finish our nutrition project I will propose to the staff that we adopt the plan.

I gather that the essayists have not used a placebo which I think is important. I am also curious as to how they know whether or not the patients take the stilbestrol.

Is there a possibility that the basic radicle of stilbestrol may be the agent producing their good results rather than the estrogenic factor?

DR. GEORGE VAN S. SMITH (Closing).—Dr. Page raised the question of some unconscious selection of patients. We were not trying to sell stilbestrol; we were trying to find out whether our idea was correct. The selection of patients was made by an elderly, retired, primary school teacher; she had had no experience whatever with medical problems; one woman looked just like another to her as regards pregnancy. The reason why we had more controls is simply that in the rushing prenatal clinic it was impossible for one person to select accurately alternate cases; some who would have been treated got by and were later included in the controls.

Dr. Page also questioned the validity of thinking that chorionic gonadotropin is utilized for the production of the placental steroids. That chorionic gonadotropin is so utilized is still a concept which was first advanced by Drs. Browne and Venning of Montreal. We have adopted this concept, thinking it might explain the drop in gonadotropin toward the end of the first trimester, when the steroid hormones increase and when there has been no great decrease in the cytotrophoblasts which produce the gonadotropin. The

A temporary drop in pregnandiol excretion as measured by the colorimetric assay follows the initiation of stilbestrol therapy to a perfectly normal patient. This drop is due, at least in part, to a temporary effect of stilbestrol in lowering the excretion of non-specific chromogens. It disappears in a few days and is followed by a steady rise. This initial drop is accompanied by an immediate marked rise in the excretion of sodium pregnandiol, this rise being due, at least in part, to an increased excretion of pregnanolone. There is no question, therefore, on the basis of the findings of three independent investigators, all of whose results are in agreement provided they use the same methods, but that stilbestrol is having a profound and immediate effect upon the excretion of progesterone metabolites. And the findings of all three are in keeping with our original hypothesis, namely, that more progesterone is being produced.

DR. OTTO SCHWARZ, St. Louis, Mo.—I was interested in the increased weight of the babies of the stilbestrol-treated patients. I would like to ask the authors whether they watched the birth weight after the initial loss in these babies and compared this in children of controls, indicating that there might be an increase in the fluid rather than in structure in these babies. Is there an increase in amniotic fluid with these babies? I did not hear anything about why these children should have increased weight; however, it may be due to actual increase in circulation due to additional estrogen stimulation.

Recently I examined some forty specimens of pregnant uteri to study the condition of the veins and arteries. I found that at twelve weeks there is marked hyperplasia and hypertrophy of the veins and arteries. This increase continued until about the beginning of the third trimester. The vessels in the third trimester did not decrease in size but histologically there was a change, the active proliferation began to lessen to a considerable degree and the cell structure of the wall was changed back to the more usual type of cell. It may be that when stilbestrol is given this procedure may cause the vessels to keep their patency up sufficiently to cause a definite increase in body weight and in size.

DR. WILLARD M. ALLEN, St. Louis, Mo.—I would remind you of two observations: In the nonpregnant rabbit the administration of estrogen prevents involution of the corpora lutea. The corpora lutea will remain functional for a month or six weeks when estrogen is given whereas they normally function for only twelve to fourteen days. In pregnancy the situation is equally interesting: the administration of estrogen is very deleterious to the fetus. In early pregnancy estrogen will prevent implantation or produce abortion, and during the later stages it leads to death of the fetus. The dead fetuses are not aborted, however, because the administration of estrogen causes the corpora lutea to remain functional. Estrogen will completely suppress the mechanism of delivery. These findings support the theory that estrogens alter the capacity of the corpus luteum to put out progesterone. (G. P. Heckel and W. M. Allen: *Endocrinology*, 24: 137, 1939.)

There is one other point that may be pertinent. Estrogens do effect the uterine muscle. Estrogen stimulates the uterus of the nonpregnant rabbit to undergo rhythmic contractions. The uterus of a nonpregnant rabbit is responsive to Pituitrin. The administration of progesterone to castrated rabbits makes the uterus nonresponsive to Pituitrin but when exposed to both estrogens and progesterone such a uterus, when suspended in a water bath, shows a very interesting response to Pituitrin; when Pituitrin is added the uterus stops contracting and becomes atonic. The response to Pituitrin is, therefore, conditioned by the type of hormones to which the uterus has been subjected: the uterus under the influence of estrogen responds to Pituitrin by tetanic contractions, the uterus under the influence of both estrogen and progesterone responds to Pituitrin by relaxing.

It seems to me quite probable that the beneficial effects which stilbestrol exerts can be explained by assuming that stilbestrol either enhances the production of progesterone or that it produces a more favorable balance between estrogen and progesterone, thereby permitting relaxation of the uterine muscle so that the uterus itself can better accommodate the growing fetus.

# A STUDY OF THE PLACENTA IN PREGNANCY TREATED BY STILBESTROL\*

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AS A part of inquiries by Drs. G. V. and O. W. Smith into the effects of stilbestrol therapy in pregnancy, an analysis of weights of babies and placentas in treated and control series has been carried out. Gross and microscopic observations were also correlated in an effort to determine any stilbestrol effect upon the placental morphology. The primiparous full-term material included 188 cases treated with stilbestrol and 92 control cases, all primiparous pregnancies having normal deliveries without late pregnancy complications. Primiparous premature deliveries and toxemias were also investigated and will be discussed later.

Baby weights in 73 per cent of full-term control cases and 58 per cent of stilbestrol cases were between 3,000 and 3,600 grams (6 pounds, 4 ounces, and 7 pounds, 8 ounces). In the weight range over 3,800 grams (7 pounds, 15 ounces) there were 19 per cent of control cases, 27 per cent of stilbestrol cases. This indication of a larger number of heavier babies in the stilbestrol cases is the only finding significantly different in the full-term groups (Table I).

TABLE I. PERCENTAGE INCIDENCE OF FULL-TERM BABY WEIGHTS IN KILOGRAMS

Weight in kg.	2.4	2.6	2.8	3.0	3.2	3.4	3.6	3.8	4.0	4.2	4.4	4.6
Stilbestrol %	0	3.2	9.2	11.3	11.3	16.2	19.5	11.9	11.3	1.6	1.1	1.1
Controls %	1.1	3.3	3.3	17.6	16.5	22.0	16.5	4.4	6.6	6.6	1.1	0

Comparison of placental weights in the two groups revealed no definite differences (Table II).

TABLE II. PERCENTAGE INCIDENCE OF FULL-TERM PLACENTA WEIGHTS IN KILOGRAMS

Weight in kg. below	0.4	0.4	0.45	0.5	0.55	0.6	0.65	0.7	0.75	0.8
Stilbestrol %	1.6	8.1	8.7	21.1	13.0	19.0	12.4	10.0	3.2	2.7
Controls %	1.1	7.8	10.0	13.3	19.0	22.2	13.0	10.0	1.1	2.2

Ratio of baby weight to placenta weight is an index of relative maturity.<sup>1</sup> Comparison of this ratio in the two groups showed no variation indicating any distinct trend (Table III).

Gross and microscopic investigations of the placentas have been tabulated. Relative amounts of subchorionic fibrin deposition, placental calcification, and

\*Presented in part, as a discussion of the paper read by the Drs. Smith at the Seventy-Second Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 16 to 18, 1949.

slight rise of gonadotropin toward the end of gestation, when the cytotrophoblasts have practically disappeared, we conceive to be due to a failure of utilization by the degenerating syncytium.

Dr. Schwarz asked if the infants of stilbestrol-treated mothers continue to lose weight after their initial loss. Actually our "initial loss" figures represent the *total* loss prior to the increase in weight after delivery.

We were not told by the delivering obstetricians of any increase of amniotic fluid in relation to the use of stilbestrol.

The greater length of more of the babies of stilbestrol-treated mothers is indicative of actual growth rather than of any water retention.

Dr. Reis asked if stilbestrol might make big babies bigger in the diabetic patient. We do not know the answer to that question because our experience with diabetics has been small, but it is safe to say that Dr. Priscilla White has not found that the babies of diabetic mothers treated with stilbestrol were too large compared with the ordinary large baby of diabetic mothers.

Dr. Kosmak inquired about the dosage schedule. This is included in the paper to be published and is practically the same as that already published in the November, 1948, issue of the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY*.

Dr. Dieckmann asked about the use of placebos, undoubtedly for its psychologic effect. We have not used them. However, I have felt that the frequent interviews with the interested and kindly school teacher might have been reassuring and done something to help these patients. Dr. Dieckmann also asked about the basic radicle of stilbestrol being the stimulating factor. That was our original idea and our reason for using stilbestrol. From our evidence in studying estrogen metabolism, we think that the stimulating molecule is not estrogenic but that the estrogen is changed and thus becomes a factor which stimulates the secretion of progesterone and estrogen, either through the pituitary gland or through enhancing the utilization of chorionic gonadotropin.

Dr. Wilson inquired when stilbestrol treatment was initiated: 75 per cent of our patients started therapy between the twelfth and sixteenth weeks; the other 25 per cent started therapy between the sixteenth and twentieth weeks of pregnancy.

and thirteen control premature births (Table V) showed that stilbestrol therapy was accompanied by increased placental weight. Eighty-four per cent of the stilbestrol series weighed over 400 grams and 54 per cent of the controls.

TABLE V. PERCENTAGE INCIDENCE OF PREMATURE PLACENTAL WEIGHTS IN KILOGRAMS

Weight in Kg.	0.3-0.4	0.4-0.5	0.5-0.6	0.6-0.7
Stilbestrol %	17	42	25	17
Controls %	46	23	23	8

This difference indicates that a heavier, presumably larger placenta is associated with stilbestrol treatment. The ratios of babies to placental weights was compared for the two premature birth groups (Table VI).

TABLE VI. PERCENTAGE INCIDENCE OF PREMATURE BABY/PLACENTA WEIGHT RATIOS

Ratio baby to placenta	4.5	5	5.5	6	6.5	7	7.5	8
Stilbestrol %	17	29	4	25	8	0	4	13
Controls %	8	15	15	0	8	38	15	0

Note that 75 per cent of stilbestrol baby to placental ratios were 6.0 or less, while 61 per cent of control ratios were 6.5 or more. This means that while with stilbestrol the premature baby and placenta are both heavier, the weight increase of the placenta is relatively greater.

Gross and microscopic findings as before were tabulated for the two groups of premature placentas (Table VII).

TABLE VII. PREMATURE PLACENTAS

	STILBESTROL (PER CENT)	CONTROLS (PER CENT)
Subchorionic fibrin:		
<i>Amount:</i> Small	51	45
Moderate	29	30
Marked	7	0
Calcification:		
<i>Amount:</i> Small	37	35
Moderate	4	0
Marked	7	5
Hemorrhage:		
<i>Amount:</i> Small	51	50
Moderate	37	20
Marked	4	0
Chorionic villi:		
Immature	40	70
Mature	59	30
Senile	0	0
Infarcts	26	15
Intervillous thrombi	29	5
Nontoxic separation	0	30
Circummarginate	37	10
Circumvallate	10	10

The most striking statistical differences found are the increased proportion of circummarginate placentas, the relative frequency of mature villi and intervillous thrombi among the premature stilbestrol placentas, and the absence of cases of premature, nontoxic placental separation after stilbestrol. If nontoxic placental separation follows some degenerative change of decidua, then stilbestrol appears to counteract it. Despite earlier maturation of trophoblast, it was not possible to find any specific histologic changes caused by stilbestrol.

A group of eight cases of toxemia of pregnancy occurring with stilbestrol therapy was compared with twenty-one untreated control toxemic cases. Due

TABLE III. PERCENTAGE INCIDENCE OF FULL-TERM BABY/PLACENTA WEIGHT RATIOS

Ratio baby to placenta below	4	4-4.5	4.5-5	5-5.5	5.5-6	6-6.5	6.5-7	7-7.5	7.5-8	Over 8
Stilbestrol %	0	1.6	6.0	18.3	22.0	13.4	16.1	11.3	7.0	4.3
Controls %	1.1	2.2	11.1	11.1	14.4	17.7	12.2	7.7	11.1	3.3

hemorrhage were recorded. Presence of significant numbers of immature, mature, and senile chorionic villi was noted. The incidence of the diagnosis of placental infarction, intervillous thrombosis, and nontoxic premature separation of placenta was noted. The findings are compared in Table IV.

TABLE IV. FULL-TERM PLACENTAS

	STILBESTROL (PER CENT)	CONTROLS (PER CENT)
Subchorionic Fibrin:		
<i>Amount</i> : Small	35	40
Moderate	46	46
Marked	9	9
Calcification:		
<i>Amount</i> : Small	61	67
Moderate	18	16
Marked	11	5
Hemorrhage*:		
<i>Amount</i> : Small	40	54
Moderate	26	26
Marked	7	5
Chorionic villi:		
Immature	17	13
Mature	82	86
Senile	1	1
Infarcts	21	17
Intervillous thrombi	25	16
Nontoxic separation	8	11
Circummarginate	27	9
Circumvallate	5	2

\*As evidence of premature separation.

Grossly, circummarginate stilbestrol placentas are three times as frequent as found among controls. The only other differences apparent are twice as many cases of marked calcification in the full-term stilbestrol series as among the controls, and more frequent intervillous thrombosis in the stilbestrol group in a ratio of three to two. Both changes are indices of marked aging in some stilbestrol placentas.

Histological study of the whole group of full-term placentas and comparative retrospective analysis have not shown any differences characteristic of stilbestrol therapy in the placenta. It is noted that no stilbestrol was administered during the last three to four weeks before delivery. If a difference existed, it may already have disappeared at the time of delivery. Also, the withdrawal of stilbestrol may have exaggerated placental aging, and encouraged the marked calcification and intervillous thrombosis occasionally observed.

A comparable investigation was made of placentas of twenty-seven premature births, of thirty-eight weeks' or less gestation, with stilbestrol therapy and twenty premature births without treatment. The gestation periods were mostly thirty-five to thirty-seven weeks' duration, and twins were excluded.

Statistical investigation of this group by the Smiths has already shown that premature infants born after stilbestrol therapy are larger than control infants. Comparison of placental weights of twenty-four stilbestrol premature infants



## ETIOLOGY OF ECLAMPSIA\*†

### I. Water Balance

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DESPITE expert unlimited obstetric and dietetic care we have not been able to prevent the development of pre-eclampsia and an occasional case of eclampsia in our patients. The incidence of pre-eclampsia over a period of years has remained relatively constant but the number of severe cases has decreased. The eclampsia is apparently not severe in that there have been no deaths for many years but we have had similar experiences in the past with, sooner or later, death resulting. We believe our improved results are due to early recognition by the doctors and the nurses of too rapid weight gain which results in the patient being referred to the toxemia clinic where she is under expert care. Failure to improve necessitates hospitalization and, after study and treatment for varying periods of time, termination of the pregnancy.

The senior author<sup>1</sup> has been interested in the etiology, diagnosis, and treatment of pre-eclampsia and eclampsia for over twenty-five years and has made many studies during this period. Unfortunately, complete chemical and physiologic studies on the same patients had not been made because of a lack of personnel. It has only been during the past year that a partially complete staff for research has been available. Just recently a beam balance, sensitive to 1.0 Gm. for weighing patients, and an air-conditioned room for reproducing various climatic conditions, has become available. We believe that pre-eclampsia and eclampsia differ only in the occurrence of convulsions and/or coma in the latter condition. We also believe that these conditions are clinical entities peculiar to the pregnant woman.

The senior author<sup>2</sup> some years ago obtained data on the incidence of eclampsia from various parts of the world. There seems to be no doubt that where native people have little association with civilization, the incidence of eclampsia is very low or the condition does not occur. He also showed that a hot, humid climate in the United States was associated with the highest incidence of eclampsia. Theobald<sup>3</sup> reports a very low incidence of severe toxemia in Siam and a very high incidence in Ceylon, both countries having a similar climate.

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to the small number of cases and disparity of numbers, detailed statistical analysis is not possible. The difference in incidence of toxemia with and without stilbestrol therapy may be the most notable discrepancy. Five of seven stilbestrol babies weighed over 2,700 grams (5 pounds, 10 ounces) and nine of twenty-one control babies were in this weight range. In the stilbestrol group, three of seven placentas weighed over 600 grams, while only three of twenty control placentas were as heavy. Relative distribution of ratios of baby weight to placental weight was similar for stilbestrol and control toxemic groups, but no finer interpretation seemed desirable.

Gross and microscopic study was made as noted before. It was of interest that five of eight stilbestrol-treated toxemia cases had circummarginate placentas, and none of the controls, although two of twenty-one control toxemia placentas were circumvallate. Other factors such as subchorionic fibrin, calcification, and hemorrhage occurred with equal frequency and in similar quantities in both groups. Relatively senile syncytial trophoblast and "Tenney changes" associated with toxemia<sup>2</sup> were noted in one-fourth of placentas in each group. Thrombosis of decidual sinusoids was observed in half the stilbestrol-treated toxemia placentas, twice the frequency encountered in toxemia controls. Intervillous thrombi were seen in half the stilbestrol and one-fifth the control toxemia placentas. Infarcts were more common in the stilbestrol placentas in a ratio of five to four. None of these findings appear to demonstrate clear-cut morphologic differences in the stilbestrol-treated cases associated with toxemia, and review of slides from stilbestrol and control groups confirmed this.

### Summary

A statistical investigation has been made of effects of stilbestrol therapy in pregnancy upon weights of baby and placenta. Changes in gross and microscopic placental structure due to stilbestrol have also been sought. Stilbestrol-treated and untreated control groups of primiparous full-term and premature births, as well as cases with toxemia of pregnancy, have been included.

Evidence is presented that weights of both baby and placenta are increased in stilbestrol-treated full-term and premature births and in the toxemia group. Ratios of baby weight to placental weight were the same for stilbestrol and control groups in the full-term and toxemia cases, and were decreased in the stilbestrol-treated premature birth group. Stilbestrol stimulates increase in weight and presumably size of both infant and placenta. One by-product of placental overgrowth found is an increased proportion of circummarginate placentas in all three stilbestrol groups, as compared to controls.

Gross and microscopic study indicated more frequent occurrence of marked placental calcification and intervillous thrombosis in full-term stilbestrol-treated placentas. In premature stilbestrol-treated cases there was similarly a higher incidence of mature chorionic villi and intervillous thrombi. No nontoxic premature separations were encountered after stilbestrol therapy. The toxemia cases with stilbestrol therapy more frequently had thrombosis of decidual sinusoids and intervillous thrombi than controls, but the number of such cases was small. No specific histologic change was observed which was attributable to stilbestrol treatment.

### References

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in that we have not been able to cause any increase by various substances and methods which normally raise blood pressure. The diastolic pressure in the eclamptic and severe pre-eclamptic patient is unusually high, differing from the patient with essential hypertension in whom the diastolic pressure only becomes high late in the disease. The substance causing the vasoconstriction has been assumed to come from the placenta, the kidney, the intestinal canal, the adrenal gland, the pituitary, etc.

Grollman<sup>8</sup> states that it remains to be proved that hormonal aberration is the cause of toxemia and not the result of some fundamental process.

A number of investigators<sup>9, 10</sup> have reported that proper nutrition, implying an adequate amount of protein and of vitamins and not too many calories, has prevented the onset of eclampsia in their patients and some even claim the prevention of pre-eclampsia. We are analyzing the results of a large well-controlled nutrition study in which there was an adequate number of dietitians to properly supervise the patients and calculate diets, and chemical technicians to analyze blood and urine. There was supplementary protein (milk powder or meat) given without charge and yet some of our patients with good nutrition records not only developed pre-eclampsia but one had eclampsia. It is too early to state whether or not we have decreased the incidence of pre-eclampsia by dietary supervision.

Since there are no pathologic lesions peculiar to eclampsia and since the Goldblatt kidney does not produce eclampsia, we believe that animal experimentation is of no value in determining the etiology of eclampsia. We have, therefore, for some years limited our studies to the pregnant patient.

Many investigators believe that there is first a salt and water retention due to an abnormal capillary permeability. Some of the patients develop a hypertension (which may be compensatory), proteinuria, which may be due to edema of the kidney or to vasoconstriction, and a very few have various other symptoms and signs due to cerebral anoxia, again the result of edema or vasoconstriction, culminating in convulsions and coma, or both. This theory seems the most reasonable and is the one which we are now investigating. We are also accumulating other pertinent data. Our purpose is not to bolster up some preconceived idea of the cause of eclampsia.

We do not know the cause of pre-eclampsia-eclampsia but we hope we can determine the etiology, the diagnosis by some chemical or physiologic test, the prevention, and the proper treatment if recognized soon enough. Our studies seem to indicate that pre-eclampsia and eclampsia are a disturbance in the normal physiology of various organs and tissues which, if not too great, readily returns to normal. It could be compared to early shock which is a recognizable condition due to a decrease in the blood volume which, if treated early enough, is easily curable, but if neglected too long becomes irreversible because of pathologic changes and therefore is not amenable to any treatment. Certain cases of eclampsia can last so long that pathologic changes have occurred which cannot return to normal.

Since we have been using procedures which should increase the severity of the case, we have been impressed by the fact that many patients do not get worse

The woman with access to the grocery store has table salt and baking soda in pound containers and uses both freely in cooking and at the table. She eats too much, drinks too little, and urinates and defecates when convenient for her—not when nature signals. Many women worry about finances, marital difficulties, the pregnancy, etc. The primitive native woman has many diseases but she escapes the overabundance of food and condiments, the habits and living conditions of her civilized sister, and she rarely has eclampsia.

Our studies indicate that the periportal hemorrhages, occasional necrosis, or very rare anemic infarct of the liver, are peculiar to the pregnant woman under certain conditions but are not pathognomonic of eclampsia. Likewise, our studies and those by Canny<sup>4</sup> indicate that thickening of the glomerular capillary basement membrane is not characteristic of eclampsia but occurs in a high incidence of pregnant patients. Thus there is no pathologic lesion either in the liver, kidney, or any other organ characteristic of eclampsia.

Several reports<sup>5, 6</sup> indicate that there is no abnormal renal physiology in eclampsia. This is difficult to believe. However, it should be noted that none of the studies were made during the oliguric or anuric phase of the disease.

Various liver function studies<sup>7</sup> show impairment during severe pre-eclampsia and a rapid return to normal after delivery.

The disappearance in some patients within hours after delivery of all signs and symptoms indicates an abnormal physiology of various organs (liver, kidney, brain, etc.) rather than pathologic lesions which would require a much longer time for a return to normal. Likewise the fact that so many various types of treatment result in the same relatively low mortality, providing no drastic procedures are instituted which of themselves entail a high maternal mortality, also indicate that there is no irreversible abnormal physiology present in most eclamptic patients.

Eclampsia only occurs if normal or hydatidiform villi are attached to the uterine wall (either intrauterine or extrauterine). So far as we know there are no reported cases of eclampsia in patients with chorionepithelioma. Improvement takes place early after death of the fetus but a return to the normal only occurs when all the placental tissue is removed.

We question the published reports of patients who are normal one day and within twenty-four hours or less have eclampsia, occasionally terminating fatally. Many conditions can cause convulsions or coma. Some of these reported cases may be due to accidental or intentional poisoning, to essential hypertension, or to some dozen other diseases. When we know the cause of pre-eclampsia and have some positive criteria for the diagnosis, such cases will be even rarer than they now are.

Vasoconstriction does not seem to be the cause of eclampsia because most of the patients have no absolute or relative hypertension at the onset of their pre-eclampsia. If vasoconstriction is the cause then many of these patients should ultimately have a systolic blood pressure greater than 200 mm. Hg and the severity of the eclampsia should parallel the height of the blood pressure. Our experience is that the majority have systolic blood pressures under 200 and, as a rule, less than 180 mm. Hg. Furthermore, these blood pressures are fixed

A vast literature<sup>11, 12</sup> has accumulated during the past two decades on the importance of water for the normal functioning of the body. Extracellular water comprises some 20 per cent of the body weight and intracellular amounts to 50 per cent. Furthermore, water is contained in various compartments, namely, the vascular system, the skin, muscle, brain with a fibrous (dura) and bone capsule; the kidney and the other organs, all with capsules. Obviously a positive water balance will cause increased pressure within these various organs including the brain with its bony walls, thus producing many of the serious symptoms and signs associated either with an excess or a decrease in the normal amount of water within or between the cells.

Water is absolutely essential for life. Too much or too little, depending upon the climate, soon produce systemic changes which if continued may terminate in death in a few hours to several days. A failure of water to reach the kidney even though there may be anasarca is more dangerous than absolute dehydration. Edema may be a protective mechanism for a time. These physiologic changes, together with alterations in weight as well as various symptoms and signs, may be obvious within an hour. The longer the abnormality in water balance persists, the greater the changes in the body.

Haldane and Priestly<sup>13</sup> in 1914 noted in experiments on themselves that excessive drinking of tap water could result in dizziness, vomiting, and an unpleasant sense of fullness. If the hydration continues, convulsions, coma, hypertension, anuria, and death will occur. These observations have been made by various observers.<sup>14</sup> Periodic ingestion of water together with repeated injections of posterior pituitary solution have been suggested by McQuarrie<sup>15</sup> and others as a therapeutic test for epilepsy.

The normal kidneys can excrete up to 1200 ml. of urine per hour for a short time but owing to fatigue the diuresis soon decreases to approximately 750 ml. per hour.

A number of investigators<sup>1</sup> using various tests have demonstrated that there is a delayed excretion of water in pregnant patients which is greatly intensified in severe pre-eclamptic patients. Edema of varying degree occurs in approximately two-thirds of normal pregnant patients.<sup>16</sup> Oliguria or anuria are characteristic of eclampsia and persistence of these signs is associated with increasing mortality.

Janney and Walker<sup>17, 18</sup> administered 200 ml. of water every thirty minutes from 9:00 to 11:30 A.M., and compared the volume of urine from 9:30 A.M. to 1:00 P.M. with the average output of 1353 ml. of the nonpregnant normal individual. At term, normal pregnant women excreted only 67 per cent. The average for toxemic patients was 17 per cent. A significant finding was that the horizontal side position gave the highest water excretion throughout pregnancy, amounting to 99 per cent. The Trendelenburg position in the same patient gave 66 per cent, the dorsal position 55 per cent and the sitting position 32 per cent. The studies by Smirk<sup>19, 20</sup> showing that the lower half of the body acts as a water depot, and the observations of numerous investigators on the increased venous pressure due to the arteriovenous leak through the placenta and the pregnant uterus pressing on the abdominal veins, offers a logical explanation why the horizontal side position should give the highest urinary output in the pregnant woman.

but even improve on such management. We are speculating with the idea that certainly at the onset there is no toxin circulating in the blood in pre-eclampsia but that the condition is merely the result of a body which has not been able to eliminate water, electrolytes, and possibly other substances as it should. In some patients this may be due to an inherent weakness to excrete electrolytes and in such individuals edema may recur with each pregnancy. We have learned that many patients with pre-eclampsia are not in such a delicate balance that the proverbial straw will precipitate eclampsia. ✓

We are making a very extensive study of pre-eclampsia using as many chemical and physiologic measurements as personnel permits. Treatment is not being neglected as various therapeutic procedures are also being tried. If we were attempting to prove some "pet" theory, our investigative work would cost less and would be much simplified. Many analyses are useless on account of labor beginning or being induced for safety of the patient and baby, specimens are lost, or the study proves valueless.

We are determining plasma and extracellular fluid volume. We realize that all determinations, and these in particular, are subject to an inherent error but believe they may show relative changes. We hope to determine total body water. We now have accurate weights in our patients which we consider of the utmost importance. The volume of the lower extremities is being determined to detect water retention. Water, sodium, potassium, chloride, and nitrogen balances are being made. Serum and urine proteins and their fractions are being determined. Renal and liver function studies are made. Liver and kidney biopsies are being obtained when feasible. Hemoglobin, hematocrit, nonprotein nitrogen, urea nitrogen, uric acid, free and combined cholesterol, and other blood constituents are being determined repeatedly in the same patient. We are determining the antidiuretic hormone in serum and urine in certain cases and the urinary corticoids. Certain tissue enzymes and capillary permeability have been determined.

Various procedures such as repeated injections of plasma, of large amounts of purified serum albumin, injections of pitressin, desoxycorticosterone acetate, ingestion of thiamin chloride, of the B-complex, heparin, isotonic and hypertonic solutions of sodium chloride, solutions of  $\frac{1}{6}$ th molar sodium lactate, glucose solutions, and other experimental, diagnostic, and therapeutic measures are being carried out. We have been amazed to find that many presumably pre-eclamptic patients have been able to tolerate the sodium ion, either orally or intravenously, in large amounts without any clinical manifestation as long as they were able to eliminate it in the urine and the chloride intake was less than one gram per twenty-four hours. A very few patients have not only gained weight rapidly but have developed the characteristic findings of severe pre-eclampsia, namely, headache, dizziness, diplopia, decrease in vision, increase in blood pressure and proteinuria, as the result of the overloading with sodium chloride solution. Water alone or in the form of intravenous glucose solution can, if given in sufficient amount, produce convulsions and coma. Injections of solution of posterior pituitary<sup>1</sup> favor water retention and apparently have precipitated the onset of convulsions in patients with pre-eclampsia.

the patient probably has Addison's disease provided that nephritis has been excluded. We add that pregnancy must also be excluded. The water factor was abnormal in 40 per cent of the pre-eclamptic patients, both ante partum and post partum. Comparable figures for patients with essential hypertension are 12 and 17 per cent, respectively; for normal pregnant patients 17 per cent and 0, and for nonpregnant 9 per cent. The means are given in Table II. The marked difference between patients with pre-eclampsia and essential hypertension is evident and is primarily due to the low hourly urines characteristic of pre-eclampsia. The means for the pre-eclamptic patients were 24 before delivery and 99 in the same patients after delivery, indicating a marked difference in water, sodium chloride, and urea metabolism. The patients with essential hypertension in pregnancy had a factor of 194 before and 159 after delivery. They could not only excrete water better than the pre-eclamptic patients but had a slightly higher concentration of urea in the urine, and with the lowered blood urea in pregnancy, the factor naturally was greater.

TABLE II. WATER FACTOR

	PRE-ECLAMPSIA		ESSENTIAL HYPERTENSION	
	ANTE	POST	ANTE	POST
MEAN	24	99	194	159
$P_s = 0.9$	16	79	99	93
S.D.	36	200	288	315

$P_s = 0.9$  = indicates that in 9 out of 10 cases the true value of the mean is between these limits.

The hourly urine volume is shown in Fig. 1. The difference between pre-eclampsia and essential hypertension in the ante-partum group is quite marked. Many of the pre-eclamptic patients had either no urine or very small amounts within the first few hours. Some of the hypertensive patients also had small volumes in the first hours but it is possible that our diagnoses were wrong or that these patients had an essential hypertension with a superimposed pre-eclampsia. It is quite obvious that the pre-eclamptic patient, before delivery, has a markedly impaired water metabolism which has shown a marked improvement by the tenth post-partum day. The patients with essential hypertension show a distinct difference from the pre-eclamptic patients in their ability to excrete water. Our data is still being analyzed but it looks as if one could state that if the patient has a urinary output comparable to that found in essential hypertension, she does not have pre-eclampsia. However, if the output is decreased within the limits for pre-eclampsia, she might have either or both conditions.

Typical cases illustrating ante-partum and post-partum urine volumes are given in Fig. 2. Both the patients with essential hypertension had the condition before pregnancy. The pre-eclamptic patients have not been followed through another pregnancy but have all the other criteria which would seem to support the diagnosis.

In addition to the water clearance factor, we obtained the percentage of water excreted in the same period of time by dividing the urine output from 9:00 to 12:00 by 1,200. Fig. 3 illustrates this data. Here again it is quite apparent that a difference exists in the water metabolism in pre-eclamptic patients as compared with the same patients after delivery, with pregnant patients with essential hypertension and with normal subjects.

Odell and co-workers<sup>23</sup> on our service have given pregnant patients 1,000 ml. of 5 per cent glucose intravenously within a twenty-minute period. Urine was collected in six consecutive fifteen-minute periods. They stated that normal pregnant patients, not in labor, excreted 100 to 125 per cent during the second

Theobald and Verney<sup>21</sup> have studied the urine output during pregnancy. They found that toward the end of pregnancy women secrete an increasing proportion of urine by night so that the night-to-day ratio may exceed unity. Their explanation is that in the upright posture fluid escapes into the tissues and returns only when the individual is at rest in the horizontal position. Muscular exercise of the legs prevent some, but not all, of the filtration. If the fluid thus lost to the tissue by day becomes so excessive that it cannot all be reabsorbed during the night, edema of the tissues, commencing in the lower extremities, will occur.

Bed rest has resulted in some shifting of fluid from the lower extremities but not in complete subsidence. The inflatable suits worn by dive bomber pilots to prevent blackout were loaned to us by the Navy and we could decrease the size of the legs but could not fit them to the thighs of pregnant patients. Pressure bandages are more applicable to the legs than the suits but we have not been able to adjust them to the thighs. It seems fairly certain that an increased pressure about the legs and thighs will decrease the edema.

Robinson, Power, and Kepler<sup>22</sup> devised a "water test" for determining whether or not patients had Addison's disease. We applied this test to a large number of pregnant toxemic patients, not because we thought they might have Addison's disease, but because the adrenal gland is associated with sodium and water balance and certain standards had been established. The test briefly consists of two parts:

1. A comparison of hourly urine specimens after a test dose of water with the urine volume for the preceding nine hours. If the volume of the largest hourly specimen is less than the night urine, the response is positive, that is, Addison's disease may or may not be present.

$$2. \text{Water factor} = \frac{\text{urea in night urine}}{\text{urea in plasma}} \times \frac{\text{chloride in plasma}}{\text{chloride in urine}} \times \frac{\text{volume of largest hourly specimen}}{\text{volume of night urine}}$$

There was so much nausea and vomiting produced by the administration of 20 ml. per kilo body weight that we decreased this amount to an arbitrary 1,200 ml., which was drunk between 7:00 and 7:45 A.M.

The data for patients who had less urine in the morning hourly specimens than in the night urine are given in Table I. Eighty-two per cent of the pre-eclamptic patients and 48 per cent of those with essential hypertension had an abnormal ratio before delivery, that is, a positive test.

TABLE I. RATIO OF MAXIMUM HOURLY URINE TO NIGHT SPECIMEN. ABNORMAL PER CENT

PRE-ECLAMPTIC		ESSENTIAL HYPERTENSION		NORMAL PREGNANT		NONPREGNANT
ANTE	POST	ANTE	POST	ANTE	POST	
82	35	48	32	33	33	13

Robinson and collaborators stated that if the water clearance factor was more than 30, or if any of the morning hourly specimens were greater than the night urine, the patient did not have Addison's disease. If it was less than 25



urine collection, that is, within 30 minutes from the time of the completion of the injection. Normal patients, early in labor, excreted from 10 to 70 per cent, usually in the third and subsequent periods. Pre-eclamptic patients, not in labor, excreted from 10 to 35 per cent in the third or consecutive periods. Thus, after the intravenous injection of 5 per cent glucose, there is an appreciable decrease in the total amount of urine eliminated, as compared with the normal, and a marked delay in the onset of the diuresis. This study indicates that the delayed excretion is not due to faulty absorption of water in the intestinal tract.

We have all observed eclamptic patients, with no demonstrable edema at the initial examination, within a few hours develop edema of such magnitude that the eyes are closed and the legs pit easily. Since the patient had not been given any fluid, the only source was from her own tissues, where it could have been intracellular.

The senior author<sup>24</sup> in 1940 suggested that "A large amount of water could be held in the muscle cells of the body without the patient showing any demonstrable edema. This phenomenon would account for those patients whose weight gain is so rapid that it must be due to a retention of water and yet no edema can be detected. Furthermore, if this water were quickly released from the cells, it would account for the sudden appearance of edema noted in some eclamptic patients, and for the occasional development of symptoms and signs of acute cardiac decompensation in toxemic patients." He presented a typical case in which there was a negative balance after delivery for sodium, potassium, and chloride.

Thompson and Pommerenke<sup>25</sup> in three pregnant women reported an average retention of 14.7 meq. of sodium and 7.9 meq. of potassium. Coons and co-workers,<sup>26</sup> report a daily mean retention in normal pregnant patients of 0.877 Gm. of chloride, 1.265 Gm. of sodium, and 0.508 Gm. of potassium.

Intravenous injections of deuterium oxide<sup>27</sup> into the guinea pig indicate that 73 per cent of the plasma water is exchanged every minute and that the deuterium oxide comes into equilibrium with approximately 65 per cent of the body weight. Thus water in the body is in a dynamic state; the concentrations of sodium and potassium, both intracellular and extracellular, effect its distribution.

Furthermore, several reports<sup>28, 29</sup> indicate that there are variations in the amount of sodium, potassium, and chloride in intracellular and extracellular fluids.

It is conceivable that the severe type of eclampsia is due to an excessive amount of intracellular water and electrolyte.

Bardeleben<sup>30</sup> cut up a frozen body and found that the legs and thighs comprised 37.2 per cent of the total weight. We have not been able to devise any method for weighing the extremities in pregnant women. Smirk was able to show an increase in the weight of the lower extremities after drinking water and a persistence of the weight indicating that the lower extremities acted as a depot. It is true that the legs and thighs can contain a huge amount of fluid without showing pitting edema. This fluid may be intracellular and we have studies in progress to determine the extent and frequency of this type of water and electrolyte retention. We have been immersing patients to the middle of the thigh in a large metal container and determining the volume by the displacement of water. We find that there may be a decrease in the leg volume by the tenth post-partum day amounting to as much as 6 L., representing a decrease in leg volume of 36 per cent. Various studies<sup>31, 32</sup> indicate that the placenta acts as an arteriovenous shunt, thus accounting for the increased venous pressure in the legs which begins at the fourth month, reaches a maximum at term and rapidly returns to normal after delivery. In the last trimester of pregnancy the venous pressure in the lower extremities is much greater because of the added pressure of the pregnant uterus on the large abdominal veins.

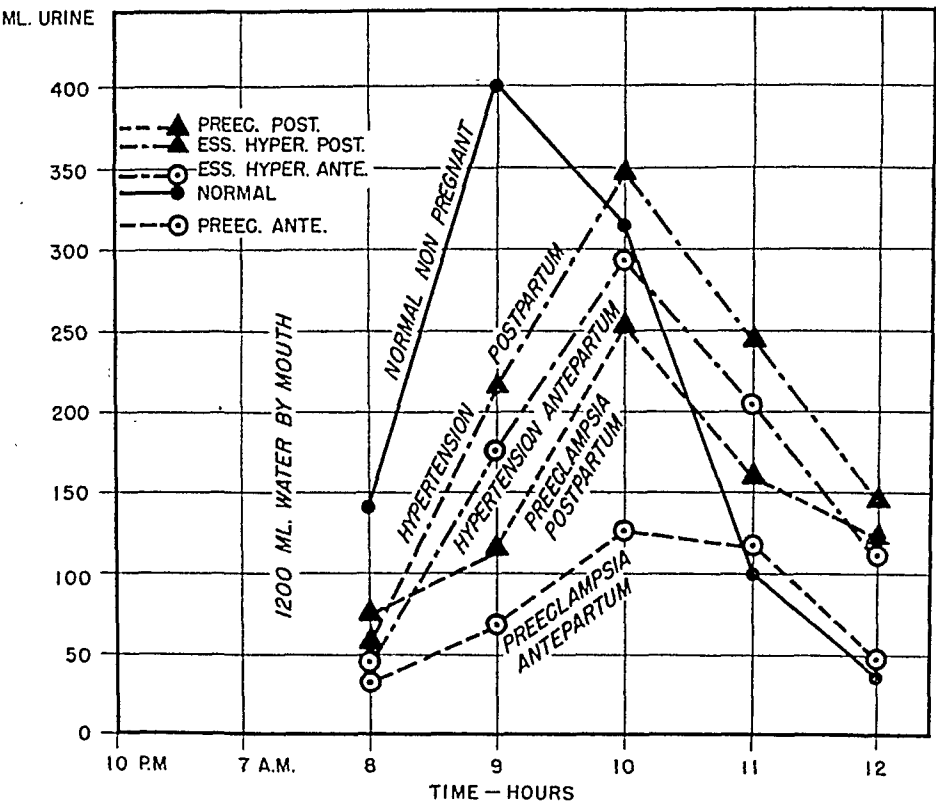


Fig. 1.—Mean hourly urine volume for adrenal function test. Note effect of pregnancy and, in particular, pre-eclampsia in delaying time of diuresis and decreasing urine output.

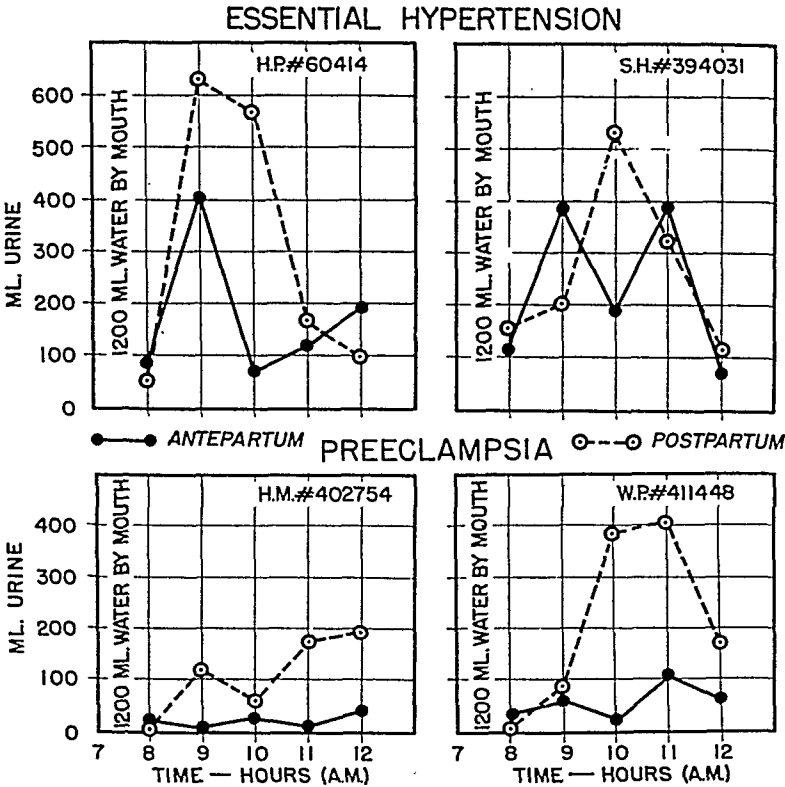


Fig. 2.—Adrenal function tests ante partum and post partum. Note effect of pre-eclampsia before delivery.

antidiuretic secretion of the neurohypophysis is a hormone in the physiological sense, that its liberation is mainly and continually governed by the contemporary concentration of sodium chloride in the carotid arterial plasma. Changes within the range and of the order of 1 per cent in the osmotic pressure of the arterial blood lead, through the intermediation of the A.D.S., to changes in the rate of water excretion within the range and of the order of 1,000 per cent: the maintenance of near constancy in the osmotic pressure of the internal environment is thereby achieved."

Verney states, "The post-pituitary A.D.S. is released in the living animal by two distinct agencies, emotional stress and an increase in the osmotic pressure of the arterial blood. On the assumption that the A.D.S. in post-pituitary extract has, on reaching the kidney, the same structural form as has that released endogenously, this release is shown to be inhibited or suppressed by an increase in sympathetic activity associated with the animal's discomposure."

According to Smith,<sup>37</sup> the evidence is not conclusive but apparently the major portion of the reabsorbed water due to the action of the antidiuretic substance takes place in the thin segment of the kidney tubule. If the antidiuretic substance is in excess, the excretion of ingested or parenterally injected water is delayed from two to ten hours and it produces a slight and variable increase in the excretion of chloride. It is incapable of accelerating the reabsorption of water if the concentration of salt in the urine is very great. Verney has shown that the membrane of the osmoreceptor is a selected one in that certain substances, for example, sodium chloride, produce a marked secretion of antidiuretic substance while other substances such as glucose and urea produce little or no secretion.

Smirk, in an ingenious experiment in human beings, has shown that after the ingestion of 1,000 ml. of water an increase in the weight of the abdomen is observed, at once followed by a gradual decrease. It requires from twenty-two to fifty-five minutes for the absorption of 1 L. of warm water which occurs best about three hours after a meal. His experiments also show that the weight of the leg and the thigh increase after the ingestion of water and that there is a lag in the decrease in weight of the lower extremity indicating that the lower extremities have acted as a depot.

Various reports<sup>38, 39</sup> indicate that the hormones of the adrenal cortex and thyroid gland, through effects on electrolyte and water excretion, renal function, permeability, etc., have an important regulating influence on the metabolism and distribution of body water.

The pregnant woman has a delayed excretion of water, sodium, and chloride which may be due in part to the increased deposition and delayed absorption caused by the high venous pressure in the lower extremities as well as to changes in the pituitary and adrenal hormones. Our preliminary studies seem to indicate that if there is a constant diuresis, thus preventing any stimulus for the release of antidiuretic substance, the urine volume will remain fairly constant. However, if the antidiuretic substance increases, there is a delay in the normal individual which becomes exaggerated in the toxemic patient, thus accounting for the oliguria or anuria. Other factors may be involved in the decreased excretion of urine but it seems most probable that the antidiuretic substance is the important one. Additional evidence is found in several reports which show that the parenteral injection of solution of posterior pituitary results in the smallest volume of urine per hour, frequently even an anuria of several hours' duration, in patients with pre-eclampsia. We have not been able to find any data as to the mechanism by which alterations in concentration of the antidiuretic substance occur.

The average venous pressure in the legs at term is 20 cm. and for the arm veins is 9 cm. of water. Landis<sup>33</sup> has shown that fluid accumulates in the tissue spaces when the venous pressure is greater than 15 to 20 cm. of water. A certain amount of protein leaks through the capillary walls, returning to the circulation by the lymphatics. Drinker<sup>34</sup> reports that fluid from a leg lymphatic of a dog contains 0.5 to 2.1 Gm. per cent protein. Protein in the interstitial fluid would attract more water and delay its absorption. Thus, on simple physiologic grounds one can account for a large retention of fluid in the normal depots where reabsorption is delayed in the normal individual. Since the accumulation of extracellular water is accompanied by a retention of sodium and chloride and a probable intracellular retention is accompanied by a retention of sodium, potassium, and chloride, the so-called physiologic edema of most pregnant patients can be accounted for. Studies reveal that some subjects require a longer period to eliminate given amounts of water, sodium, and chloride.

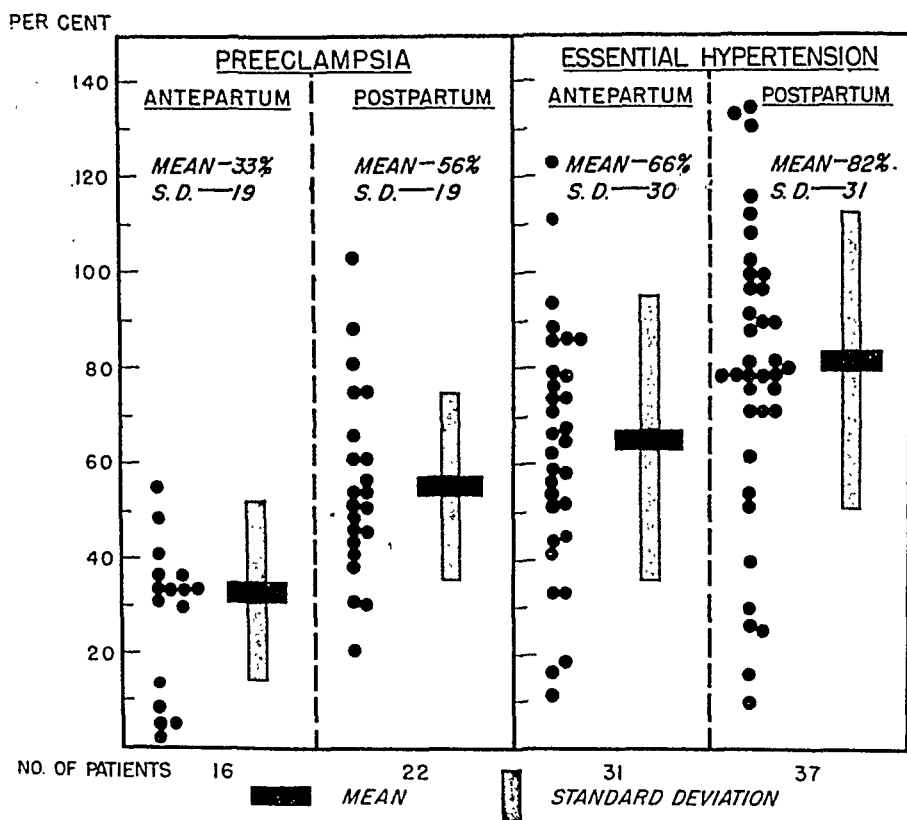
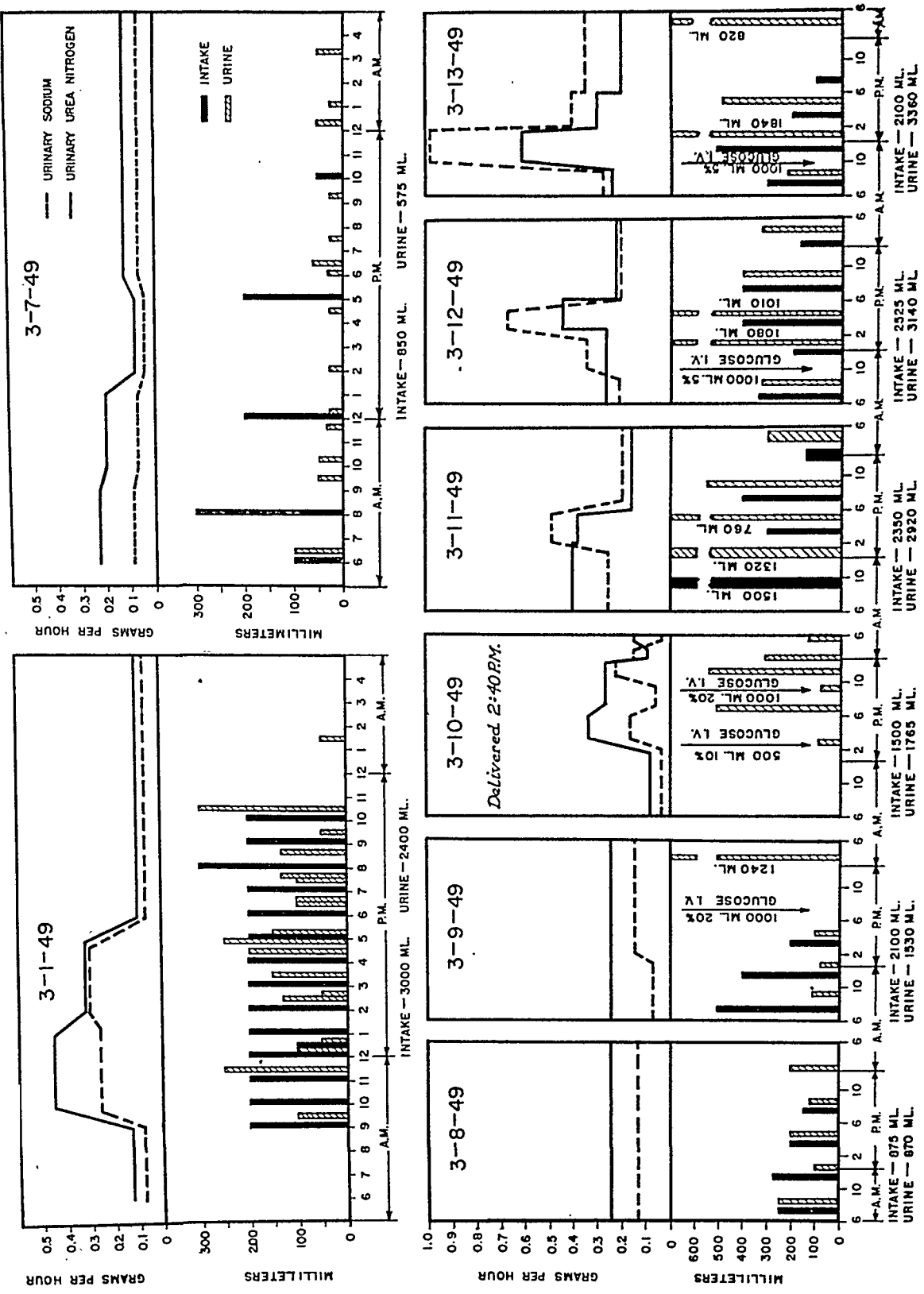


Fig. 3.—Means standard deviations and frequency distributions for percentage of water excreted. Note low figure for ante-partum pre-eclampsia and marked scatter, as well as large, standard deviation.

Any abnormal condition which interferes with water or cellular metabolism will intensify the normal delay in water and electrolyte excretion. Some of these factors are anemia, a slight decrease in the concentration of serum albumin, multiple pregnancy, polyhydramnios, cardiac disease, etc.

The stimulus to urinary secretion of water is an excess amount in the blood of water or of one of the electrolytes or nonelectrolytes. The excretion of water by the kidney is dependent upon a relatively abrupt blood dilution and a decrease in the concentration of the antidiuretic substance (A.D.S.) in the blood. Hart and Verney<sup>35</sup> conclude that a fall in the concentration of the antidiuretic substance of less than one part of substance in fifteen billion parts of the plasma will result in a spontaneous diuresis. Verney<sup>36</sup> states, "Water diuresis is a condition of physiological diabetes insipidus, and there can be little doubt that the



Newburgh<sup>40</sup> demonstrated that the optimum amount of urine requiring the least work for the normal kidney is approximately 2,000 ml. per twenty-four hours. He did not state whether the major portion of this urine should be excreted in a few hours or over a major portion of the day. Several observers have reported that the quantity of water lost in a diuresis due to water excess may be greater than the quantity taken in.

Wolf<sup>41</sup> has had ten normal subjects drink 20 to 200 ml. of water per ten-minute periods for as long as seven hours. The urinary output alone was 8 per cent greater than the intake.

The data in Fig. 4 on W. J. D. demonstrates that the excretion of water, sodium, urea, etc., can be maintained at a higher level with a greater total elimination for twenty-four hours if measured amounts of water are ingested at hourly intervals. Incidentally, the subject is much more comfortable under this regime.

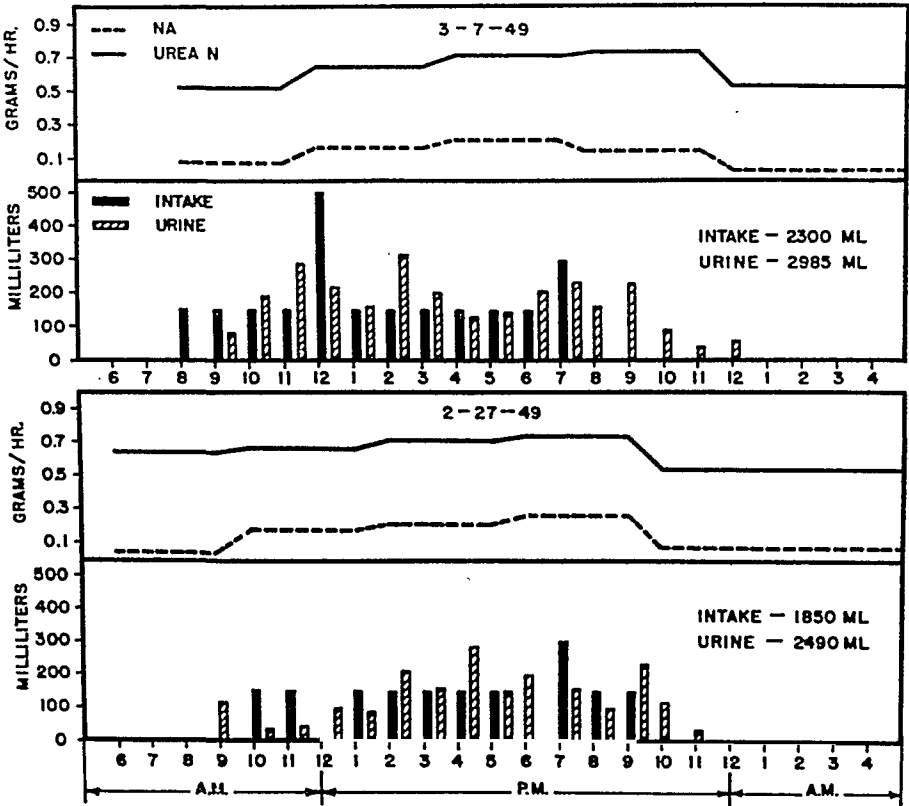


Fig. 4.—Water, sodium, and urea nitrogen balances for two days on subject W. J. D. Note increased output during periodic ingestion of water.

S. S. No. 452429, for whom pertinent data are given in Fig. 5, is a typical case of pre-eclampsia. Unfortunately, but probably best for her safety, she went into labor before our studies were completed. She was able to excrete sodium, chloride, and water while taking fluids at regular intervals Fig. 5 (day 1), but when left to her own choice the intake and output decreased to dangerous levels (days 7, 8, 9, 10). It is quite obvious that if such a course of events is continued for some days there will be a marked accumulation of water and electrolyte in the interstitial spaces and the beginning of a vicious circle (further increases in the venous pressure, edema of kidney, increased cardiac work) which causes a still greater delay in water and salt elimination. Intravenous glucose, even in 5 per cent concentration, produced a diuresis and an increase in sodium, chloride, total electrolyte, urea and nonprotein nitrogen excretion. The diuresis and elimination of retained water and electrolyte which began within forty-eight hours after delivery is typical of

7 kg. increase in weight and an increase in the interstitial fluid of 9,870 ml. and of 1,722 ml. in plasma volume without any evidence of edema. This same patient had a maximum decrease of 23 per cent in the plasma protein concentration and a 21 per cent increase in the total amount of circulating plasma protein, thus indicating that there are stores of plasma protein presumably in the interstitial fluid.

These observations of Stewart and Rourke indicate a possibly new type of therapy for the markedly edematous patient, namely, a continuous injection of 5 per cent glucose solution for several days or longer.

### Summary

We have not been able by obstetric and dietetic care to reduce the incidence of pre-eclampsia or prevent the development of an occasional case of eclampsia.

The elimination of water given by the oral or intravenous route is delayed in all pregnant patients but more markedly in those with pre-eclampsia than in those who have hypertensive disease. This delay may be due in part to the increased storage of the water in the legs and thighs as a result of the high venous pressure in the lower extremities due to the pregnancy.

The antidiuretic substance from the posterior pituitary and the hormones from the adrenal cortex are also involved but the mechanism of control is still in doubt.

A urinary volume of 2,000 ml. per twenty-four hours is recommended as requiring minimal work by the normal kidney. The hourly ingestion of water in constant amounts of 150 to 200 ml. seems to produce better elimination of water, electrolyte and nonelectrolyte substances than the irregular ingestion of large amounts.

It seems advisable to instruct normal patients not to ingest more than 1 to 2 Gm. of sodium, 4 to 6 Gm. of chloride, and 1 to 2 Gm. of potassium per twenty-four hours during pregnancy.

We wish to thank Miss F. Dunkle (Chief dietitian) and the various residents, nurses, and technicians who have assisted in the various studies and experiments.

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these cases (days 11, 12, 13). The delivery results in a marked and immediate decrease in the venous pressure in the lower extremities where large amounts of water and electrolyte have been retained, thus making these substances readily available for excretion.

We believe that there is sufficient evidence indicating that where there is evidence of extensive peripheral edema, there is also an increased amount of water in the kidney with its tough capsule, thereby probably adding an additional impediment to renal work. The amount of water in the liver is presumably also increased with a resultant impairment in its function to detoxify substances absorbed from the intestinal canal and brought to it from other portions of the body. An increased amount of fluid both inside and between the brain cells may have quite drastic results. One effect may be an increase in the amount of antidiuretic substance or a failure in its removal or neutralization. A small increase in the intracellular or extracellular fluid of the brain will result in an increased irritability and other symptoms and signs associated with anoxia of the brain, namely, headache, dizziness, diplopia, nausea, and vomiting which may terminate in convulsions. A still greater increase will result in coma, hyperpyrexia, and death.

We have studied three pregnant patients with diabetes insipidus who, while not taking pituitary solution or powder, developed edema of the legs. Two had marked edema and hypertension despite volumes of urine ranging from 3,000 to 6,000 ml. per day. Immediately after delivery the edema and hypertension subsided rapidly.

The plan of prophylaxis and of treatment based on Newburgh's observation and our own studies indicates that the pregnant woman should ingest sufficient tepid or cool water with a low sodium, chloride, and potassium content every hour throughout the day and evening in sufficient quantities to yield approximately 2,000 ml. of urine in twenty-four hours. Obviously, in hot, dry weather, she will have to drink more than in cold weather. She should also be taught to decrease the amount of sodium, chloride, and potassium ingested in her food because once these substances are in the body there is some delay in their excretion, even by the normal individual. The maximum concentration of sodium, chloride, or potassium in the urine is 0.7 per cent, 1.1 per cent, and 0.5 per cent, respectively. A normal adult will excrete approximately 5 Gm. of sodium, 11 Gm. of chloride, and 3 Gm. of potassium in the twenty-four-hour urine.

Schwarz and Dieckmann<sup>42</sup> in 1929 stated that intravenous injections of 20 per cent glucose solution would produce an increased excretion of chloride in the urine. We have sufficient data now to show that if enough glucose solution is administered intravenously, the total amount of sodium per hour is definitely increased. Several observers have reported that in nonpregnant subjects intravenous glucose administration will produce an increased elimination of sodium. Stewart and Rourke<sup>43</sup> have shown that the continuous intravenous injection of 5 per cent glucose solution to relatively normal post operative patients over periods ranging from 36 to 144 hours not only resulted in an increased elimination of sodium in the urine but caused a diminution in the volume of the extracellular fluid of 1,960 ml. in one patient. One patient actually became comatose because of the decreased concentration of sodium in her blood and tissues. In other words, she suffered from water intoxication although she was dehydrated. Another patient was given 0.9 per cent sodium chloride with a



should also be reckoned as intake. Furthermore, large quantities of water leave the body by way of the lungs and skin. These items of intake and output may amount to over a liter per day.

But even disregarding these niceties of precision it is apparent that water is stored. Hydremia, inordinate gain in weight, and suppression of urinary output is gross evidence of this water storage. As much as 6,000 c.c. of water can be stored without gross evidence of edema. Edema, therefore, is obvious evidence of even greater storage of water. The legs can thus become veritable reservoirs of water as well as fat.

Because the amount of water stored, notably the edema, is often seemingly out of proportion to other clinical manifestations of toxemia, and because with some patients having severe toxemia, edema may not be a conspicuous feature, I wonder if Dr. Dieckmann would care to comment further on any parallelism between the degree of edema and the severity of pre-eclampsia.

One other question: if failure to eliminate water adequately is a feature of pre-eclampsia, would one not wish to consider the use of stronger diuretic measures than the administration of some 2,000 to 2,500 c.c. of water per day?

DR. J. ISFRED HOFBAUER, Cincinnati, Ohio (by invitation).—For the past few years the primary significance in the etiology of late toxemia of pregnancy of the remarkably altered endocrine pattern was put in clear perspective. The demonstration of the occurrence during the last trimester of gestation of a distinct increase in the number and secretion of basophils in the adenohypophysis, hypertrophy of the adrenal cortex with urinary excretion of corticoids in the order of amounts found in the urine of individuals suffering from Cushing's syndrome, increased response of the arterioles to the postpituitary principle and to adrenalin entail potential hypertensive factors, while the vasodepressor effect of placental acetylcholine apparently represents the neutralizing principle concerned with the maintenance in normal gestation of a delicately balanced blood pressure equilibrium. In toxemia, due to significantly higher placental cholinesterase levels and its resulting low acetylcholine content and choline deficiency in the blood, a dislocation of the balanced opposition of contrary stimuli on the vasomotor function ensues, with hypertension as the main sequel.

It is now an accepted fact that hormones play important parts in water metabolism and in the exchange and function of sodium, chloride, and calcium. As an early manifestation of choline deficiency, impairment of the oxidative metabolism occurs (Abdon and Berglin) and, according to a recent announcement by Best, choline deficiency may be an etiologic factor in the mechanism of hypertension. Direct association of heightened activity of the adrenals as playing a genetic role in toxemia is suggested by last year's report of a significant increase in the urinary output of corticosteroids. Recent identification in three pre-eclamptics of our series of nonadrenalin assumes particular interest in view of the demonstration by Bulbring and Burn that splanchnic stimulation can result in the liberation of this power transmitter of constrictor impulses.

DR. GEORGE VAN S. SMITH, Brookline, Mass.—Dr. Dieckmann's paper again brings to my mind the same thought I have had for years: that there is an analogy or similarity between normal pregnancy and toxemia and the phenomenon of menstruation. For years I have puzzled as to what morphologic similarity there could be between these processes. Dr. Hertig has recently given me the answer. He states that decidual necrosis is a constant feature of human gestation, normal and abnormal. This means to me that a menstrual-like process plays a role in normal and abnormal pregnancy. Although Dr. Olive Smith and I have become associated with the idea of abnormal hormonal balance in relation to toxemia, actually our thinking is in terms not of hormones but of the menstrual phenomena.

I would inject another thought. We know that once the uterus is removed from the nonpregnant woman, normal ovaries being left, there are no signs to indicate changes in ovarian hormonal levels. Very little objective study has been done on such women but what has been done gives no evidence of ovarian hormone withdrawal in the absence of the endometrium. In other words, it is not the hormonal withdrawal which ultimately

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## Discussion

DR. W. T. POMMERENKE, Rochester, N. Y. (by invitation).—Those of us who know Dr. Dieckmann and have had the privilege of hearing his presentation are aware of the fact that for years he “has been living intimately with the toxemias of pregnancy.” Therefore his comments, born of this long association, are deserving of serious consideration.

Specific predictions in medicine are frequently hazardous. Dr. Dieckmann hints—with a voice that is perhaps too faint—that factors which some may regard as psychosomatic and sociologic may be operative in the etiology of eclampsia. I venture the prediction that we will hear more concerning this aspect of the practice of medicine in the years to come. Many will regard as novel the view, as again expressed by Dr. Dieckmann, that there are no renal or hepatic lesions pathognomonic of eclampsia. Repeated needle punch biopsies of the liver and kidneys should in time establish the validity of this belief.

Researches on the so-called toxemias of pregnancy have been historically linked with and bottlenecked by the search for some phantom toxin. Dr. Dieckmann suggests that pre-eclampsia and eclampsia may have their bases in a deranged physiology rather than in frank pathology. New technologies may, therefore, be expected to furnish necessary information on which to base proper concepts of this disease, or shall we call it “metabolic state.” Of these Dr. Dieckmann speaks with enthusiasm and hope.

Would it not be ironic if the long-sought toxic substance turned out to be water? Certainly the immodest imbibition of water by man and beast will produce symptoms, even convulsions, presumably due to cerebral edema, which we associate with severe toxemia.

Pregnancy is a period of rejuvenescence and of growth. It is characterized by storage of large quantities of nitrogen, electrolytes, and water. Let the philosopher argue the import of this storage. The fact is that chemical analyses seem to indicate that this storage is far in excess of actual needs for tissue construction of the fetus.

Water balance studies must take into consideration, in addition to obvious water taken in as such and the quantity of urine eliminated, the fact that there are other significant quantities of water intake and output. The water in food, measurable by dehydration, and that found within the body by the oxidation of fats, carbohydrates, and proteins

# Department of Reviews and Abstracts

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## Selected Abstracts

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### Newborn

Fox, M. J., Krumbiegel, E. R., and Teresi, J. L.: Maternal Measles, Mumps, and Chicken-pox as a Cause of Congenital Anomalies, *The Lancet*, page 746, May 15, 1948.

Various clinical studies have shown that congenital anomalies (cataract, heart disease, deaf-mutism, and dental abnormalities) follow early pregnancy rubella at fifteen times the ordinary rate. The only other virus effect thus far investigated is that of poliomyelitis, fetal anomalies being present in two infants of 98 cases collected. Both of these cases followed poliomyelitis in the first four months of gestation, of which there were 24 cases in all.

In a survey of sixty thousand cases of measles, mumps, and chicken pox occurring in Milwaukee in 1942 to 1945, the authors found six cases of measles, twenty-three cases of mumps, and four cases of chicken pox in pregnant women. Only one of the thirty-three infants had an anomaly; a congenital harelip following measles in the fourth month of pregnancy. This series is admittedly too small to prove anything, especially since only four patients were infected during the first eight weeks of pregnancy. From a negative standpoint, it is disclosed that 76 children, conceived from three weeks to four years after one of these diseases, had no malformations. Conception soon after rubella, however, has been reported to eventuate in defective infants.

IRVING L. FRANK.

Swan, C.: Rubella in Pregnancy as an Aetiological Factor in Stillbirth, *The Lancet*, page 744, May 15, 1948.

Questionnaires answered by 760 mothers of stillborn babies disclosed that 16 of these women had had German measles during pregnancy, two having also had mumps, and a third chicken pox in the same pregnancy. No other infectious disease had a comparable incidence in these ill-fated pregnancies. In seven of the sixteen cases there was no known lethal factor present. Most significantly, in 13 of the cases, rubella had occurred during the first four months of pregnancy, the so-called "critical period." It is, therefore, suggested that rubella in early pregnancy may cause damage to the embryo eventuating in stillbirth.

IRVING L. FRANK.

Unsigned Editorial: Foetal Death or Defect From Maternal Infections, *The Lancet*, page 760, May 15, 1948.

German measles during early pregnancy often is followed by fetal defects such as cataract, heart disease, deaf-mutism, and dental and mental abnormalities. A cataract is likely to follow infection at six weeks of pregnancy, deafness at nine weeks, and a cardiac abnormality at five to ten weeks. That these defects follow infection in early pregnancy suggests a specific effect of the virus on the developing embryo.

Reliable estimates of the probability that defect, abortion, or stillbirth will follow German measles are essential in deciding the advisability of therapeutic abortion. Swan suggests compulsory notification of all infectious diseases occurring in pregnant women, interroga-

accounts for the systemic changes of menstruation but the ensuing endometrial catabolism. By analogy, decidual catabolism probably accounts for many of the normal and abnormal systemic changes in pregnancy.

DR. DIECKMANN (Closing).—We believe animal experimentation in pre-eclampsia-eclampsia is of no use. We are concentrating our studies and our experimental procedures on pregnant patients. We have no pet theories which we are trying to prove. We are not making many endocrine studies. I hope the staff will be willing to take up the use of stilbestrol according to the Smith method.

Dr. Pommerenke mentioned the effects of water. There is sufficient evidence now available which shows that too much or too little water is very definitely dangerous to life. The entire syndrome of pre-eclampsia-eclampsia can be produced by giving too much water or by large amounts of water and sodium chloride. A small amount of solution of posterior pituitary will hasten the development of the clinical condition. There are other factors. We do not think that pre-eclampsia-eclampsia is merely water intoxication. Furthermore, every pregnant woman who has convulsions or coma does not a priori have eclampsia. There are over a dozen conditions that have caused convulsions and/or coma in both pregnant and nonpregnant women. All obstetricians have had patients who either gained or lost tremendous amounts of weight (20 or more kilograms) and yet have shown no edema. We believe that patients can have abnormal retention of water and electrolytes without clinical edema. Our studies were all started in the post-partum period, and as we have gained familiarity, the various experimental procedures have been instituted in the ante-partum period.

*(The remaining papers presented at this meeting will be included in the December issue.)*

## Complications of Pregnancy

**Bazan, J., Uranga Imaz, F. A., and Fernandez, J. A.:** Acute Leukemia and Pregnancy, *Obst. y ginec. latino-am.* 7: 145-164, May, 1948.

The authors describe in detail a case of acute myelogenous leucemia in a 24-year-old woman who was five months pregnant. Her leucemia was initiated with an abrupt clinical onset—serious and rapidly progressive anemia, irregular febrile course, ulceration of tonsils, pronounced capillary fragility, gingival hemorrhage, slight hepato- and splenomegaly and ultimate loss of vision. A therapeutic abortion and supportive therapy failed. The patient died two and one-half months after interruption of pregnancy.

The authors, after an extensive review of eighty-eight cases in the world literature, conclude that leucemia is a contraindication to pregnancy and that management of such cases is the joint responsibility of the obstetrician and the hematologist. CLAIR E. FOLSOME.

**Portes, L., and Granjon, A.:** Amniotic Puncture and Amniography, *Gynec. et obst.* 47: 42-48, 1948.

Portes and Granjon, of Paris, do not consider the puncture of the amnion, via the abdominal transectaneous route, dangerous, while providing certain advantages in selected instances. The removal of excessive liquor amnii in acute polyhydramnios permits the carrying of pregnancy up to a more suitable period of viability of the fetus. In selected cases of therapeutic abortion, the addition of artificial serum, 300 to 600 c.c., to the amniotic cavity is recommended. The changing tonicity of the fluid content with increasing pressure initiates onset of labor. In cardiac, tubercular, and renal contraindication to pregnancy the authors find this method less traumatic than interruption from below. Similarly, the onset of labor, in cases with dead fetuses in utero, can be hastened. If labor does not begin within forty-eight to seventy-two hours, a second amniotic intracavitary injection is given of 200 to 300 c.c.

For amniographic studies the authors use a 20 or 40 per cent aqueous iodized solution as used in urography. These solutions are diluted with artificial serum and injected with a 50 c.c. syringe. Under the fluoroscope the authors have used the amniographic shadows to study uterine contractility and incidentally the action of certain pharmacodynamic drugs upon uterine contractility. The injected iodized solution was eliminated rapidly in the urine of the mother. Four pictures of roentgenograms are included in the article. CLAIR E. FOLSOME.

**Ledesma, Domingo:** Colpocytology in Hyperemesis Gravidarum, *Bol. Soc. de obst. y gynec. de Buenos Aires* 27: 23-26, April 15, 1948.

The author, upon the premise of Anselmino's that hyperproliferemia frequently accompanies a deficiency of estrogen in degenerating moles, chorionepithelioma, and hyperemesis gravidarum, decided to evaluate this observation by use of vaginal smears. Thirty-two cases of hyperemesis were compared to six nonpregnant cases and twenty normal pregnancies, each six months pregnant. He found that the squamous cells were predominantly acidophilic in the nonpregnant group. The cytology in the first trimester is the same as in the nonpregnant save for a slight increase in the number of basophilic staining cells. The cells in the last trimester of pregnancy take predominantly a basophilic stain. Those patients exhibiting hyperemesis gravidarum showed principally acidophilic staining reaction which agrees with the anticipated estrogenic deficiency and hyperproliferemia. CLAIR E. FOLSOME.

## Sterility, Fertility, Contraceptives

**Weinstein, B. Bernard:** The Surgical Management of the Tubal Factor in Sterility, *South. Surgeon*, page 556, Aug., 1948.

Tubal occlusion is the largest single sterility factor in the female. Kymographic tracings obtained under carbon dioxide insufflation permit differentiation of diagnosis into: (a) normal patency, (b) nonpatency, (c) tubal spasm, (d) tubal stenosis. Salpingography

tion of women presenting themselves at prenatal clinics, and a close follow-up of all pregnancies complicated by infections. The studies of Ober et al. indicate that rubella in the first month is followed by defect, abortion, or stillbirth in four out of five cases, four out of eight in the second month, three out of nine in the third month, and four out of twenty-seven in the last five months.

IRVING L. FRANK.

MacMahon, H. Edward: Congenital Alveolar Dysplasia of the Lungs, *Am. J. Path.* 24: 191, July, 1948.

The author describes a pathological entity involving the lungs of some full-term newborn infants showing respiratory distress and progressive intractable cyanosis. While the correct diagnosis in such cases is usually atelectasis, the primary congenital anomaly described in this paper can produce the same clinical syndrome.

Three cases are presented. In each instance the child cried and breathed promptly. There was progressive cyanosis and respiratory distress until death supervened. At autopsy the lungs were normal in size, firm, rubbery, and dark red. The main microscopic change was a predominance of interstitial tissue with far too few alveoli. The interstitial tissue failed to show well-developed mature collagen when stained with Mallory's and fuchsin-aniline blue stain.

L. M. HELLMAN.

Ellis, Richard W. B.: The Newborn: Some Problems of Survival, *Edinburgh M. J.*, page 321, June, 1948.

This paper deals with some of the factors concerned with infant wastage in Scotland. The author states that never before has the newborn received more consideration than he does in most civilized countries today. This has been brought about by the fact that the reduction in total infant mortality rate has been principally due to a reduction in death rate of infants from 1 to 12 months of age. The reduction in the death rate of infants under one month has shown very little change from 1911 to 1946. The ratio of neonatal to postnatal deaths for the quinquennium, 1911 to 1914, was 43:71. In 1946 this ratio was 26:26. The better survival rate of females over males is pointed out. The higher infant wastage rate in illegitimate births is considered. Certain factors which may improve this infant loss in this group are discussed. These are improvements in the birth certificate so that the illegitimacy of the infant is not disclosed and improvement in the adoption laws. The question of inoculation of children born to tuberculous mothers with B.C.G. is discussed. A discussion of antenatal, neonatal, and postnatal mortality rates in 1939 and 1945 by social class is presented. It is interesting that the difference in stillbirth rate between social classes was greater in 1945 than in 1939. The question of diet in its relation to the status of the newborn infant is discussed. Some of the current literature is cited. The major causes of infant death are ascribed to prematurity, neonatal infection, intracranial hemorrhage, and congenital malformations.

L. M. HELLMAN.

Luschinsky, H. L., and Singher, H. O.: Identification and Assay of Monamine Oxidase in the Human Placenta, Reprinted from *Arch. Biochem.*, vol. 19, no. 1, Oct., 1948.

Monamine oxidase is contained in the human placenta at term. The authors prove the presence of this enzyme by a study of substrate specificity, the demonstration of the reaction products and the action of certain inhibitors. The authors state that, theoretically, about 0.7 Gm. of tyramine can be deaminated by the average placenta per hour. They state that it is probable that the monamine oxidase serves in the detoxification of amines and that, inasmuch as some of the amines are sympathomimetic in their vasomotor action, monamine oxidase in the placenta may separate the fetal from the maternal vasoactive substances and conversely the mother's from those of the fetus. Inasmuch as the activity of this enzyme depends upon partial pressure of oxygen, it may be permissible to assume that under conditions of placental ischemia the enzyme may not fulfill its physiological role, i.e., the destruction of vasopressin amines.

L. M. HELLMAN.

## Correspondence

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### Mucocele of the Cervical Stump

*To the Editor:*

In the February, 1949, number of the JOURNAL (Vol. 57, No. 2, pages 341-344) I wrote an article on "Mucocele of the Cervical Stump." This article started with the sentence, "No reference to mucocele of the cervical stump could be found in the study of the literature." Purely by accident, I just came across an article entitled "Report of Case of a Large Mucocele of the Cervix, Following a Supravaginal Hysterectomy Fourteen Years Previously," which appeared in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, Vol. 9, page 349, 1928, written by Frederick A. Cleland of Toronto, Canada. In this article Dr. Cleland states, "I have been unable to find in the literature anything similar to this specimen, . . . ." His case is identical with the one that I encountered except that the external os was completely obliterated and that the nature of the tumor was therefore not recognized. In consequence of this, a difficult but successful operation was performed from above.

In justice to Dr. Cleland, his article should be mentioned.

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### Removal of the Umbilical Stump

*To the Editor:*

For some time it has been my routine to remove the umbilical stump as early as the fifth day after birth. The procedure consists of the simple maneuver of twisting the stump off either with the fingers and a piece of gauze cord dressing, or with a hemostat. The oozing base is touched with a silver nitrate applicator, and then covered with a tincture of Merthiolate dressing.

Although this routine has been followed in well over a thousand cases, not a single instance of hemorrhage or other untoward sequela has occurred in the entire series.

I have found the procedure a worth-while service. It eliminates the occasional odoriferous stump, and avoids the distasteful chore of repeated cord dressings sometimes lasting over a period of two or more weeks. It also admits of earlier immersion baths.

A thick stump occasionally delays the procedure two or three days.

The procedure is so simple and yet so practical that I hesitate to report it. However, I have never found it mentioned in any literature or textbook, and have never seen it performed in any clinic. I heartily recommend it.

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SEPTEMBER 28, 1949

under Rayopake installation permits localization of the occluded point. An attempt to establish patency should be made by repeated injection of Lipiodol, diathermy, chemotherapy, and estrogen administration. These methods failing, surgery must be considered. The usual techniques for establishing tubal patency are reviewed, but preference is not expressed for any one of these. The author is experimenting with a sugar stick in cases of tubal resection with anastomosis. The importance of repeated insufflation following surgery is emphasized.

WILLIAM BICKERS.

Popenoe, Paul: Infertility and the Stability of Marriage, West. J. Surg., page 309, May, 1948.

Infertility is the precursor to divorce. It is estimated that the childless marriages have divorce incidence of 70 per cent; whereas, in the group of couples with even one child, the incidence of divorce falls to 8 per cent. It must be remembered that half of all the childlessness is voluntary. Among 3,013 permanently childless marriages, farmers were found to have the lowest incidence of voluntary sterility (42 per cent), while the highest incidence was found in the professional groups (57 per cent).

Some of the partners involved in childless marriages are so inferior psychologically, physically, or socially that their childlessness may be socially or eugenically desirable. In the divorced population, which is largely made up of partners to previous childless marriages, the incidence of crime, insanity, and suicide is high. Life expectancy in the divorced population is about one-half that in the married group. It must be inferred that the divorced population is biologically inferior. Proper attention to sterility factors will aid those who are socially and eugenically sound, since they are the ones usually seeking aid. WILLIAM BICKERS.

Robertson, Jarratt P.: Semen Analysis in 204 Cases of Sterile Marriage, South. M. J. 41: 537, June, 1948.

About 10 per cent of all marriages in America are barren, and it is estimated that one-tenth of these sterile matings are the result of semen defects. Adequate examination of semen includes tests of volume, viscosity, number of spermatozoa per c.c., motility, survival time, and morphology. Taking the accepted standard of 3 c.c. volume, 60,000,000 sperm per c.c., 75 per cent motile after one hour, and a viability of twenty-four hours with abnormal forms not exceeding 25 per cent, sixty-two per cent of the 204 males studied were subfertile or sterile. Absolute sterility was present in 22 males, or 10 per cent of the total. Eight female partners in the subfertile group were sterile, leaving 98 possible conceptions for the entire group. Conception occurred in thirty, eighteen of whom delivered normal children. Since there is no satisfactory therapy for the subfertile male, with the possible exception of thyroid for those with a low basal metabolism rate, it must be assumed that the thirty conceptions are at least partially the result of medical treatment directed at raising the relative fertility of the female.

WILLIAM BICKERS.